Multi-use disease models
A blueprint for application in support of health care insurance coverage policy and a case study in Diabetes Mellitus.

National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

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Colophon

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Synopsis

Multi-use disease models
A blueprint for application in support of health care insurance coverage policy and a case study in Diabetes Mellitus.

The National Health Care Institute (hereinafter referred to as ZIN) advises the Minister of Health, Welfare and Sport (VWS) on a variety of topics, including reimbursements for medicines and other treatments in the mandatory health insurance package. For this purpose, among other things, ZIN uses dossiers from pharmaceutical companies, in which they estimate the health benefits and costs based on decision models.

These decision models are used to examine whether medicines and other treatments improve the health of individuals in the long term. For example, they calculate how better blood glucose levels in people with diabetes translate to less complications, such as cardiovascular diseases and amputations. The models incorporate the costs of the medicine, but also the savings made because the medicine reduces the likelihood of complications and the resulting high treatment costs.

ZIN is currently assessing decision models dossier by dossier, with a different decision model being used for almost every medicine or treatment. Therefore, it is difficult to compare the effects of a number of medicines for the same disease. ZIN also spends a lot of time testing the quality of each decision model. It would be better to have a single model for each disease, or multi-use models, as such models meant for repeated use might be called. This would enable those involved to make better and more consistent decisions.

RIVM and the Universities of Twente, Maastricht, Groningen and Utrecht have carried out a study into how ZIN could work with multi-use models. This report will assist ZIN in making the decision of whether to switch to multi-use models and, if so, how. By way of case study, RIVM has also created a multi-use model for diabetes.

RIVM and its partners have developed five business cases for working with multi-use models and described their advantages and disadvantages. The roles and responsibilities of the parties involved, i.e. ZIN, other research institutes, academic groups, and consultancy bureaus, vary in these options. Issues discussed include ownership of the model, who is responsible for the maintenance and storage of results and who is accountable if mistakes are made. Other issues discussed concern the model methods, among others what the model must be able to do and how flexible it has to be for adaptation.

Keywords: reimbursement for medicines; decision models; effectiveness; basic package; package management

Publiekssamenvatting

Ziektemodellen voor herhaald gebruik.
Een blauwdruk voor de toepassing in het pakketbeheer en een case studie bij Diabetes Mellitus.

Zorginstituut Nederland adviseert de minister van VWS onder andere over vergoedingen van medicijnen en andere behandelingen in het basispakket van de ziektekostenverzekering. Het Zorginstituut gebruikt daarvoor onder andere dossiers van medicijnenfabrikanten waarin zij de gezondheidswinst en kosten inschatten op basis van beslismodellen.

Met deze beslismodellen wordt bekeken of medicijnen en andere behandelingen op de lange termijn effect hebben op de gezondheid. Bijvoorbeeld wat een betere bloedsuikerspiegel bij mensen met diabetes betekent voor complicaties, zoals hart- en vaatziekten en amputaties. Ook brengt het model de kosten van een behandeling met een nieuw medicijn in kaart. Denk aan de kosten van het medicijn zelf, maar ook besparingen omdat het medicijn de kans op complicaties met hoge behandelkosten kan verkleinen.

Op dit moment beoordeelt het Zorginstituut voor bijna elk medicijn of behandeling een dossier waarvoor een apart beslismodel is gebruikt. Hierdoor zijn de effecten van verschillende medicijnen voor dezelfde ziekte niet goed te vergelijken. Daarnaast is het Zorginstituut veel tijd kwijt om de kwaliteit van elk beslismodel te toetsen. Het is daarom aantrekkelijk om voor elke ziekte één model te hebben, de zogenaamde meervoudig gebruik-modellen. Hiermee kunnen betere en consistentere beslissingen genomen worden.

Het RIVM heeft met de universiteiten van Twente, Maastricht, Groningen en Utrecht verkend hoe het Zorginstituut met meervoudig gebruik-modellen kan gaan werken. Mede op basis van dit rapport beslist het Zorginstituut of en hoe zij verder gaan met meervoudig gebruik-modellen. Bovendien is een meervoudig gebruik beslismodel gemaakt voor diabetes en als casus uitgewerkt.

Het RIVM heeft vijf business cases ontwikkeld om het werken met meervoudig gebruik-modellen op te zetten, en de voor- en nadelen beschreven. In deze opties verschillen de rol en verantwoordelijkheid van betrokken partijen, zoals het Zorginstituut, onderzoeksinstituten en consultancy bureaus. Het gaat daarbij over vragen als wie eigenaar is van het model, wie verantwoordelijk is voor het onderhoud en de opslag van resultaten, en wie aansprakelijk is bij fouten. Daarnaast komt aan de orde wat een dergelijk model moet kunnen en hoe flexibel het moet zijn voor aanpassingen.

Kernwoorden: vergoeding van medicijnen; beslismodellen; doelmatigheid; basispakket; pakketbeheer

Voorwoord vanuit ZorgInstituut Nederland

De gezondheidszorg is volop in beweging waarbij steeds nieuwe interventies beschikbaar komen. Het Zorginstituut heeft als taak om de kwaliteit, betaalbaarheid en toegankelijkheid van zowel de nieuwe interventies als van bestaande interventies te waarborgen. Hierbij wordt steeds vaker de afweging gemaakt of de nieuwe interventie wel betaalbaar en kosteneffectief is. Dit hangt sterk samen met de vraag welke zorg er vergoed moet worden vanuit het basispakket. Als onderdeel van de besluitvorming over de vergoeding van nieuwe interventies uit het basispakket wordt de kosteneffectiviteit van de nieuwe interventie ten opzichte van de huidige standaardzorg bepaald door middel van een economisch model.

Een van de taken van Zorginstituut Nederland is het gevraagd en ongevraagd adviseren over de samenstelling van het basispakket aan de minister van VWS. Deze taak staat bekend als pakketbeheer. Het Zorginstituut zoekt naar nieuwe manieren om pakketbeheer waaronder die van geneesmiddelen toekomstbestendig te maken. In de huidige aanpak worden nieuwe geneesmiddelen beoordeeld ten opzichte van (meestal) de standaardbehandeling wat onvoldoende informatie geeft over de daadwerkelijk waarde van het nieuwe geneesmiddel in de klinische praktijk. Hierdoor is het erg lastig om behandellijnen en behandelstappen met elkaar te vergelijken. Deze aanpak komt hierdoor steeds minder overeen met ontwikkelingen in de klinische praktijk waar bijvoorbeeld verschillende behandelstappen (zoals binnen diabetes zorg) of behandellijnen (zoals binnen oncologie) steeds gebruikelijker zijn. Deze nieuwe ontwikkelingen zorgen voor een groeiende behoefte om het nieuwe geneesmiddel met alle beschikbare geneesmiddelen voor die specifieke indicatie te vergelijken, waarbij er ook wordt gekeken naar de kosteneffectiviteit van verschillende behandelstappen of behandellijnen. Ziektemodellen bieden de mogelijkheid om deze vergelijkingen te maken. Zo kunnen beter geïnformeerde beslissingen over de uitkomsten en kosteneffectiviteit van individuele dan wel combinaties van geneesmiddelen genomen worden.

Vanwege deze mogelijkheid om meer vergelijkingen te maken wordt er al een aantal jaar gesproken over de mogelijke potentie van ziektemodellen voor het pakketbeheer. Een belangrijke reden waarom ziektemodellen nog niet worden gebruikt is dat de huidige modellen niet per se gemaakt zijn ter ondersteuning van besluitvorming. Daarnaast zijn er nog verschillende vragen naar verschillende voorwaarden waaraan ziektemodellen moeten voldoen om geschikt te zijn voor besluitvorming.

In dit rapport zijn de resultaten te vinden van het onderzoek naar de inhoudelijke aspecten waar rekening mee moeten worden gehouden bij ziektemodellen. Daarnaast is er ook veel aandacht voor de organisatorische kant van het gebruik van ziektemodellen. Ter illustratie is hiervoor gebruik gemaakt van het diabetes ziektemodel dat gedurende het project verder is ontwikkeld en geactualiseerd. De gepresenteerde resultaten geven het Zorginstituut inzicht in de inhoudelijke en organisatorische aspecten bij het gebruik van ziektemodellen, waardoor het mogelijk is om de vraag te helpen

beantwoorden waar aan gedacht moet worden om ziektemodellen te betrekken bij het besluitvormingsproces rondom pakketbeheer.

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Management Samenvatting

Adviezen voor pakketbeheer door Zorginstituut Nederlands (ZIN) worden veelal geïnformeerd door gezondheids-economische beslismodellen. Dit betreft in ieder geval de gezondheids-economische evaluatie van nieuwe medicijnen met farmacotherapeutische meerwaarde. Het kan echter ook gaan om evaluatie van al bestaande gezondheidstechnologie in het kader van risicogericht pakketbeheer of om ondersteuning van klinische richtlijnen.

Deze gezondheids-economische beslismodellen worden gemaakt voor een specifieke casus en worden daarom vaak eenmalig gebruikt. Dit kan ertoe leiden dat er inconsistentie is tussen beslissingen door gebruik van verschillende modellen. Voorbeelden van dergelijke inconsistenties komen voor in de praktijk in Nederland en daarbuiten. Daarnaast kost het veel tijd om voor elk model een kwaliteitscheck uit te voeren, en zijn sommige kwaliteitseisen lastig op te leggen voor ad-hoc modellen. Ziektemodellen die meermalig gebruikt kunnen worden bieden mogelijk een oplossing voor deze problemen. Het voorliggende rapport helpt bij het (verder) implementeren van ziektemodellen voor meermalig gebruik door een scala aan methodologische kwesties te identificeren en te bespreken en door aanbevelingen te doen hoe hiermee in de praktijk om te gaan.

Een aantal bedrijfsscenario's (business cases) schetst hoe ZIN de implementatie van meermalig gebruik van ziektemodellen zou kunnen organiseren. Ook wordt uitgelegd welke beslissingen moeten worden genomen over modeleigendom, verplicht gebruik, licenties, modelonderhoud en opslag van resultaten. Het voorliggende rapport ondersteunt hiermee ZIN in het maken van een keuze rondom eigenaarschap en toepassingen door een uitgebreid overzicht te geven van implicaties en de voor- en nadelen van verschillende opties.

De resultaten zoals hieronder samengevat zijn behaald door gebruik te maken van een internationaal expert panel van 54 deskundigen afkomstig uit het academisch onderzoek, beleid, consultancy, en de industrie. Daarnaast is een casus uitgewerkt voor Diabetes mellitus. Voordat de business modellen worden gepresenteerd was nadere aanscherping van de terminologie nodig, alsmede inzicht in toepassingsgebieden. De term "ziektemodellen" bleek te vaag, omdat elk gezondheids-economisch beslismodel een ziekte modelleert. Daarom is gekozen voor het begrip ziektemodel voor meermalig gebruik. In het Engels: multi-use disease model.

Ziektemodellen voor meervoudig gebruik zijn een veelbelovende benadering om verschillende nadelen van het werken met beslismodellen voor eenmalig gebruik aan te pakken. Ziektemodellen voor meermalig gebruik kunnen zowel vergoedingsbeslissingen als andere vormen van pakketbeheer ondersteunen, zoals vraagstukken over gepast gebruik. De inzet van modellen voor meermalig gebruik is in theorie niet nieuw. Er zijn in de wetenschappelijke literatuur al behoorlijk wat theoretische studies en ook wel toepassingen van zulke ziektemodellen gepubliceerd, maar de toepassing ervan in beleidsondersteuning (voor pakketbeslissingen) komt nauwelijks voor.

Ziektemodellen voor meermalig gebruik vereisen zorgvuldigere oplossingen en minder pragmatisme dan modellen voor eenmalig gebruik. Zo zullen de validiteits- en transparantievereisten strenger zijn en moeten modellen flexibeler van opzet zijn. Dit laatste omdat ze geschikt dienen te zijn voor de evaluatie van verschillende gezondheidstechnologieën in bijvoorbeeld verschillende (sub)populaties. Omdat ze meermalig worden gebruikt, door verschillende gebruikers en voor verschillende beleids- of pakketbeslissingen, is de grotere inspanning die nodig is om te voldoen aan hoge kwaliteitsmaatstaven beter te rechtvaardigen. Dat betekent modellen die aan hogere eisen voldoen.

Toepassing van ziektemodellen voor meermalig gebruik heeft daarmee een aantal belangrijke voordelen. Het leidt tot meer consistentie tussen op modellen gebaseerde adviezen binnen hetzelfde ziektegebied. Daarnaast biedt toepassing van dit type modellen kansen om de validiteit, analyse van invoergegevens, documentatie, onzekerheidsanalyse, en transparantie van de modellen te verbeteren en om de betrokkenheid van belanghebbenden te vergroten. Om deze toepassing mogelijk te maken zullen wel een aantal methodologische en organisatorische vraagstukken aangepakt moeten worden. Dit rapport biedt hiervoor handvatten in de vorm van een methodologische blauwdruk en een aantal mogelijke business cases. In deze management samenvatting schrijven we veel over ZIN (ZorgInstituut Nederland), omdat zij de opdrachtgever zijn van dit rapport. ZIN heeft als agentschap onder andere een taak in het beoordelen van Health Technology Assessment (HTA)-studies voor nieuwe en bestaande behandelingen. Als zodanig is het een HTA-agentschap, net zoals onder andere HAS in Frankrijk, KCE in België, NICE in Groot-Brittannië en IQWIQ in Duitsland. De taken en bevoegdheden van deze agentschappen lopen sterk uiteen, maar allen krijgen te maken met het beoordelen van gezondheids-economische modellen. Daarom hebben we in de hoofdtekst meestal HTA-agentschap of HTA agency geschreven.

Belangrijkste bevindingen
Definitie en toepassingsgebieden
Deze bevindingen volgen uit de consultatierondes van het expertpanel.

Om te beginnen is een nieuwe definitie voor een ziektemodel voor meermalig gebruik geformuleerd, namelijk
"A health economic decision model that properly represents (part of) the dynamics of a disease trajectory to accommodate the evaluation of a range of alternative health technologies for the management of this disease. When several disease stages are included, consistent comparisons over these stages are possible."

Om deze definitie verder te verduidelijken gelden de volgende aanvullende specifieke eisen:
- Geschikt om meerdere typen beleidsvragen te informeren.
- Modellen die bedoeld zijn voor budgetary impact analyses (BIAs) zijn geschikt voor projecties van beleidsscenario's, op basis van epidemiologische parameters, zoals demografie, incidentie en prevalentie.

- Modellen die bedoeld zijn ter ondersteuning van vergoedingsadviezen, BIAs, klinische richtlijnen en zinnige zorg dienen afdoende "setting specifiek" te zijn, dankzij gebruik van lokale data.
- Modellen die bedoeld zijn ter ondersteuning van klinische richtlijnen en zinnige zorg dienen een afdoende deel van het ziektetraject te beslaan, in overeenstemming met de scope van de betreffende richtlijn/programma voor zinnige zorg.
- Geschikt voor de evaluatie van meerdere behandelingen/"health technologies", bijvoorbeeld alle relevante behandelingen voor een bepaald ziektestadium.
- Modellen die bedoeld zijn voor de evaluatie van behandelstrategieën die uit meerdere behandelstappen of -lijnen bestaan dienen rekening te houden met de onderlinge afhankelijkheid hiertussen.

Als belangrijkste toepassingen zijn gevonden: Het vergelijken van beleidsalternatieven en de ondersteuning van beslissingen over de toewijzing van middelen, inclusief vergoedingsbesluiten. Andere relevante toepassingen waren budgetimpact-analyses, en ondersteuning van klinische richtlijnen.

Business cases en organisatorische keuzes.
Deze bevindingen berusten op het verwerken van de inbreng van het expertpanel, discussie met de opdrachtgever en aanvullende verkenningen van de literatuur.

Er zijn vijf businesscases ontwikkeld die verschillende manieren bieden waarop ZIN de toepassing van ziektemodellen voor meervoudig gebruik kan organiseren en implementeren als onderdeel van de ondersteuning van het gezondheidszorgbeleid:
De vijf business cases zijn:
A. Volledig eigenaarschap ziektemodel door ZIN
B. Particulier/commercieel eigenaarschap
C. Geen specifieke eigenaar (open source)
D. Coöperatief eigenaarschap: academische samenwerking (ZIN + onderzoeksinstituut)
E. Academische partij/ander onderzoeksinstelling als eigenaar

Voordat een passende business case kan worden bepaald, moet eerst worden gekozen tussen een beperkte implementatie voor een geselecteerd aantal ziektegebieden, of een bredere implementatie. Business case A vereist waarschijnlijk aanzienlijke investeringen vooraf, die zich vooral laten terugverdienen bij een bredere implementatie van ziektemodellen voor meermalig gebruik over meerdere ziektegebieden. Tevens is voldoende modellencapaciteit en expertise bij ZIN vereist, inclusief een senior gezondheidseconomisch modelleur met een goede kennis van bestaande modellen op verschillende ziektegebieden, om de aankoop- en ontwikkelstrategie adequaat te organiseren. De andere business cases maken een meer geleidelijke implementatie van ziektemodellen voor meermalig gebruik mogelijk door samenwerking met externe partijen aan te gaan voor relevante ziektegebieden.
Een volledig eigenaarschap voor ZIN (A) of een coöperatief eigenaarschap (D) lijken het meest bruikbaar. Volledig eigenaarschap

heeft echter aanzienlijke financiële consequenties en vergt investeringen in personeel met voldoende expertise. Een coöperatief eigenaarschap biedt het voordeel dat geleidelijk een voorraad aan modellen kan worden opgebouwd en bestaande expertise wordt aangeboord. Het is ook denkbaar dat onderdelen van modellen, zoals kostenmodules, of risicofuncties verplicht worden gesteld en beschikbaar zijn via ZIN, zoals nu al gebeurt met PAID en de kostenhandleiding. Een commercieel (B) of academisch eigenaarschap (E) of open source model (C) sluiten het meest aan bij de bestaande praktijk. Bestaande ziektemodellen voor meermalig gebruik zijn ofwel eigendom van consultancy bedrijven of van academische groepen, ofwel ze zijn door de eigenaren open source gemaakt. Een open source model kan aantrekkelijk lijken, maar heeft als risico dat de controle mogelijkheden en de invloed van ZIN zeer gering zijn, tenzij er expertise aanwezig is/ wordt geworven om de open source modellen te valideren, te actualiseren en aan te passen aan de context. Bij een commercieel of academisch eigenaarschap ligt de verantwoordelijkheid voor onderhoud en validatie bij duidelijk gedefinieerde partijen, waarmee ZIN afspraken kan maken. Internationale samenwerking is een interessante manier om de kosten van een ziektemodel voor meermalig gebruik over meerdere HTA-agentschappen te verdelen en de efficiëntie ervan te vergroten. Dit vraagt onvermijdelijk om modellen die gemakkelijk aangepast kunnen worden voor gebruik in verschillende landen.

Een andere relevante bevinding is dat niet voor alle ziektegebieden modellen voor meervoudig gebruik nuttig zullen zijn. Dit zal afhangen van onder andere de ziektelast en de complexiteit van behandeltrajecten. De implementatie kan flexibeler gemaakt worden door niet zozeer hele modellen, als wel onderdelen van modellen geschikt te maken voor meermalig gebruik. Prioritering zou moeten beginnen met een overzicht van ziektekenmerken en verwachtingen over toekomstige beleidsvragen. Inventarisaties van bestaande modellen en / of beschikbare datasets kunnen vervolgens richting geven aan de (verdere) ontwikkeling van geschikte ziektemodellen voor meermalig gebruik.

Consequenties van methodologische uitdagingen.
Deze bevindingen berusten op het verwerken van de inbreng van het expertpanel, discussie met de opdrachtgever en aanvullende verkenningen van de literatuur.

Op basis van de mogelijke methodologische knelpunten bij de toepassing van ziektemodellen voor meermalig gebruik lijken business cases B (commercieel eigendom) en C (geen specifieke eigenaar, open source-modellering) risico's met zich mee te brengen. Bij commercieel eigendom betreffen deze risico's het gebrek aan transparantie en gebrek aan controle over wie toegang heeft tot het model. In het geval van open-source modellen hebben deze risico's betrekking op de validiteit en transferabiliteit -dat wil zeggen de flexibiliteit om het model aan te passen voor gebruik in een ander land dan waarvoor het is ontwikkeld-, veiligheid van vertrouwelijke invoergegevens en gebruikersondersteuning.
Methodologische uitdagingen die losstaan van de gekozen business case betreffen het belang van modulair modeleren, keuzes rond de mate van model-complexiteit, de rekentijd van het model, en keuzes rond

software voor model-implementatie. Deze spelen zowel bij modellen voor eenmalig als bij modellen voor meermalig gebruik, maar zijn prominenter aan de orde bij modellen voor meermalig gebruik, omdat deze modellen als vanzelf complexer zijn. Keuzes hierin beïnvloeden:
- De geschiktheid van modellen voor diverse toepassingen.
- De toegankelijkheid voor partijen die de modellen willen gebruiken.

Transparantie, onzekerheidsanalyse en validatie dragen bij aan de geloofwaardigheid van en vertrouwen in het model. Ook als ZIN geen eigenaar is, zal het reputatie-effect meewegen en is de validiteit en transparantie van modellen belangrijk.

Case study: Diabetes mellitus
Deze bevindingen zijn gebaseerd op de casus waarbij een ziektemodel voor Diabetes mellitus verder is ontwikkeld.

Het ontwikkelen van een ziektemodel voor meermalig gebruik is een proces dat een multidisciplinair team en voldoende tijd vereist vanwege de verscheidenheid aan activiteiten. De vereiste expertise omvat zowel kennis van wiskundige, epidemiologische als gezondheids-economische beslismodellen. Daarnaast zijn IT-expertise en communicatieve en organisatorische vaardigheden nodig om zaken als licenties en versiebeheer te waarborgen en om de betrokkenheid van belanghebbenden en communicatie over het model te organiseren. Tot slot is het ontwikkelen van een gebruikersinterface nodig om externe gebruikers het model gemakkelijk te laten gebruiken. Deze interface moet flexibel genoeg zijn voor een reeks verschillende toepassingen. De casestudy in Diabetes Mellitus leerde ons hoe verschillende methodologische kwesties in de praktijk aangepakt konden worden. Om meer te weten te komen over de verschillende businesscases, is een casestudy minder geschikt omdat de organisatorische context naar zijn aard gebaseerd is op een aanbesteed project, waarbij de contracterende partijen al afspraken hebben staan over het eigendom van de te leveren producten. We raden dan ook aan om dit verder te verkennen met onze businesscases als uitgangspunt. Zo zou ZIN meerdere partijen kunnen benaderen voor een offerte voor modelontwikkeling en onderhoud in een aantal prioritaire ziektegebieden.

Scenario voor vervolgstappen
Net als lopende ontwikkelingen rond patiënten-registers, kunnen ziektemodellen voor meermaals gebruik de rol van HTA-agentschappen versterken. Zo kan ZIN het initiatief nemen om na te gaan voor welke ziekten / ziektegebieden een ziektemodel voor meermalig gebruik nuttig zou zijn.
Na een dergelijke prioritering zou ZIN een aantal vervolgstappen kunnen zetten om tot een adequaat model te komen voor de gekozen aandoeningen. Ten eerste kan worden gezocht naar bestaande modellen, die actueel, relevant voor de Nederlandse setting en toegankelijk zijn. Wanneer een dergelijk model niet bestaat, is de volgende stap om te bepalen of een model ontwikkeld moet worden, ofwel vanaf nul, ofwel op basis van bestaande modellen (mogelijk modellen die nog niet kwalificeren voor meermalig gebruik).

Afhankelijk van de gekozen business case kan ZIN vervolgens zelf een model ontwikkelen / aanpassen (A), derden benaderen voor modelontwikkeling (B, C, E), of starten met een samenwerkingsproject (C, D). Het agentschap kan ook de optie overwegen om geen volledig model te ontwikkelen, maar alleen cruciale modelelementen of modules te identificeren en te (laten) ontwikkelen, en vervolgens aanbevelen dat deze worden opgenomen in elk gezondheidseconomisch beslismodel voor deze aandoening dat ZIN moet beoordelen. Ten slotte kan het agentschap ook beslissen welke belanghebbenden moeten worden betrokken en in welk stadium.

Dit alles, of het nu wordt geïmplementeerd voor een breed scala van ziektegebieden, of meer selectief voor specifieke ziektegebieden, zal helpen om de kwaliteit en consistentie van het advies van het Zorginstituut te verbeteren.

Meer details over de business cases

Zoals boven besproken presenteert dit rapport 5 business cases om ziektemodellen voor meermalige gebruik in de praktijk te implementeren. In theorie kan de keuze voor een business case per ziektegebied verschillen. Als voor een aandoening een academisch model bestaat wordt bijvoorbeeld voor academische eigenaarschap gekozen. Als er alleen een commercieel model bestaat wordt commercieel eigenaarschap gekozen, terwijl bij nieuwe modellen (geen bestaand model beschikbaar) voor eigenaarschap van ZIN wordt gekozen. Omdat sommige business cases lange termijn investeringen vergen lijkt kiezen voor variabele business cases in de praktijk geen goed idee.

Bij elke business case horen een aantal keuzes voor de organisatorische uitdagingen die het werken met modellen voor meermalig gebruik met zich meebrengt, welke hieronder per business case in meer detail worden gepresenteerd. Daarnaast geeft Tabel 1 een overzicht van relevante methodologische uitdagingen die variëren per business case. Vroege toegang tot invoergegevens, voldoende tijd en middelen voor modelontwikkeling en het bieden van gebruikersondersteuning na de ontwikkeling zijn belangrijk en onafhankelijk van de gekozen business case.

Business case A: Volledig eigenaarschap ZIN

Alle modellen waarvoor deze business case wordt gekozen hebben dezelfde eigenaar. In dit geval is verplicht stellen van gebruik een mogelijkheid. Ook is het mogelijk met (betaalde) licenties te werken, zodat er financiering ontstaat voor onderhoud en hosting. Echter, bij verplicht gebruik is het lastiger om meer te vragen dan een redelijke vergoeding van onkosten. Belangrijk is dat aansprakelijkheid goed wordt afgedekt, zeker bij verplicht gebruik. Ook preventie van misbruik is belangrijk. Hierbij is het voordeel dat ZIN als eigenaar het overzicht behoudt over het gebruik en de aanpassingen van het model en daarmee preventie van misbruik in eigen handen heeft.

Er bestaan in beperkte mate ervaringen met deze business case: Bijvoorbeeld KCE in België bouwt eigen modellen. Echter voor zover wij weten zijn deze niet ter beschikking voor gebruik door derden.

Deze business case vereist een forse initiële investering om voldoende expertise (zowel model-technisch als juridisch) in huis te hebben. Ook

zijn investeringen per model nodig voor ontwikkeling/of aankoop van een bestaand model. Daarnaast is budget nodig voor onderhoud en ondersteuning van gebruikers. Hiervoor kunnen licentie-inkomsten worden gebruikt.

Business case B: Commercieel eigenaarschap
Verschillende modellen hebben in dit geval mogelijk verschillende eigenaren. Verplicht gebruik zal lastig zijn, omdat er betaald moet worden aan een derde partij (de commerciële modeleigenaar). Er kan gewerkt worden met erkende modellen, en aansprakelijkheid ligt bij de modeleigenaar. Ook onderhoud en hosting zijn een zaak van de modeleigenaar, die hiervoor meestal met betaalde licenties zal werken. Het Zorginstituut is afhankelijk van een "derde" partij als het gaat om preventie van misbruik.
Er wordt in de huidige vergoedingsdossiers al af en toe met dit type modellen voor meermalig gebruik gewerkt, bijvoorbeeld bij medicatie voor de behandeling van Diabetes Type 2. In tegenstelling tot modellen voor eenmalig gebruik zijn dit type modellen meestal eigendom van een consultancy bedrijf en niet van een farmaceutisch bedrijf.

Deze business case vereist een beperkte initiële investering om een inventarisatie te maken van geschikte modellen. Zo nodig zou voor sommige aandoeningen een nieuw model moeten worden aanbesteed. Daarnaast is budget nodig om kennis in huis te houden over de kwaliteiten van verschillende modellen.
NB: de kosten voor aanvragers kunnen in dit scenario hoog zijn, indien licentiekosten en ondersteuningskosten hoog zijn. Daarnaast is het aanpassingsvermogen naar de gewenste context afhankelijk van de eigenaar en kan belangenverstrengeling een rol spelen.

Business case C: Geen duidelijke eigenaar (open source)
In deze business case is er geen daadwerkelijke eigenaar van modellen. Verplicht gebruik is mogelijk omdat de modellen gratis te gebruiken zijn en open source beschikbaar. De aansprakelijkheid zal in de meeste gevallen worden afgedekt met standaard bepalingen voor open source.
Er is ergens een partij/partijen nodig die de modelcode huisvest en beschikbaar stelt. Hiervoor bestaan platforms, zoals Github en CRAN (voor R packages). Dit dekt echter nog niet het onderhoud, wat daarmee een risico is. Ook preventie van misbruik is zeer lastig, omdat er niemand direct verantwoordelijk is.
Er bestaan momenteel een aantal interessante praktijkvoorbeelden, waarbij wel een duidelijk aanwijsbare modelontwikkelaar bestaat, zoals een reuma model ontwikkeld vanuit Stanford, het depressiemodel CORE, en delen van het "UKPDS outcomes" model.

Deze business case vereist een beperkte initiële investering om een inventarisatie te maken van geschikte modellen. Hoogstwaarschijnlijk zal voor sommige aandoeningen een nieuw model moeten worden aanbesteed, de vraag daarbij is dan wie dit gaat ontwikkelen, als de resultaten open source beschikbaar komen? Er is budget nodig om kennis in huis te hebben voor het beoordelen van de kwaliteit van verschillende modellen en noodzakelijke aanpassingen en ontwikkeling. Dit ligt waarschijnlijk hoger dan bij business case B, omdat er meer

eigen initiatief nodig is om de modellen te doorgronden. NB voor andere partijen zijn de kosten van gebruik laag.

Business case D: Coöperatief eigenaarschap
In dit geval kunnen de eigenaren per model verschillen, en werkt het Zorginstituut bij elk model samen met een andere partij. Deze partijen zijn gezamenlijk eigenaren van het model. Daarom is verplicht gebruik mogelijk, dankzij de betrokkenheid van het Zorginstituut als mede-eigenaar. De aansprakelijkheid kan hier een knelpunt zijn, en hierover zijn goede afspraken nodig tussen de eigenaren. Een licentie tegen betaling ter dekking van de kosten voor onderhoud en hosting lijkt een logische keuze. In principe is de ontwikkelaar en eigenaar van het model hier duidelijk aanwijsbaar, en dus de verantwoordelijke voor preventie van misbruik. Dit zal in dit scenario vooral bestaan uit goede ondersteuning aan gebruikers om misbruik te voorkomen. Voor zover bekend zijn er nog geen praktijkvoorbeelden van gedeeld eigenaarschap. Deze business case vergt initiële investeringen om modellen aan te schaffen dan wel te laten ontwikkelen. Het onderhoud en ondersteuning kunnen worden overgelaten aan de academische partijen. Deze kunnen mogelijk licentiegelden gebruiken als bron van inkomsten hiervoor. Er is een keuze mogelijk tussen hoeveel in-huis expertise wordt begroot en wat bij de academische partij(-en) wordt gelaten.

Business case E: Academisch eigenaarschap (dan wel eigenaarschap door een onderzoeksinstituut)
Ook hier kunnen de eigenaren per model verschillen. Het verplicht stellen van gebruik is lastig, omdat er "gedwongen winkelnering" ontstaat. De aansprakelijkheid dient afgedekt te worden, hiervan zijn praktijkvoorbeelden. Ook hier lijken licenties een logische manier om financiering te regelen voor onderhoud en hosting. Soms stellen academische partijen aanvullende eisen aan gebruik, bijvoorbeeld meedoen met de analyses, of invloed op toepassingen. Dit raakt aan preventie van misbruik (maar heeft mogelijk ook gevolgen voor de aanpasbaarheid van het model). Dat is in principe de verantwoordelijkheid van de model-eigenaar, en de aanvullende eis van betrokkenheid bij toepassingen kan hierin behulpzaam zijn. Voorbeelden uit de praktijk van modellen voor meermalig gebruik met een academische eigenaar zijn: het diabetes model UKPDS-OM, en de verschillende MISCAN modellen voor evaluatie kankerscreening.

Deze business case vergt een beperkte initiële investering om een inventarisatie te maken van geschikte modellen. Hoogstwaarschijnlijk zal voor sommige aandoeningen een nieuw model moeten worden aanbesteed. Het onderhoud en de ondersteuning kunnen worden overgelaten aan de academische partijen. ZIN heeft hierbij flexibiliteit wat betreft de mate van in-house expertise.

Tabel 1 Overzicht van methodologische uitdagingen en overwegingen per business case.

Business case	Flexibiliteit	Transparantie & Validatie	Toepasbaarheid in Nederlandse situatie	Toegang en gebruikersondersteuning	Toegankelijkheid en privacy	Updates en onderhoud
Volledig eigenaarschap ZIN	Onder controle ZIN	Keuze aan ZIN welke mix tussen toegang tot de code, transparante documentatie en uitgebreide validatietesten	Onder controle ZIN	Onder controle ZIN. Vergt organisatie: veilig, voldoende ICT ondersteuning, voldoende inhoudelijke ondersteuning.	Onder controle ZIN. Biedt garantie aan data-eigenaren. Vergt infrastructuur bij ZIN.	Onder controle ZIN
Commercieel eigenaarschap	Minder controle ZIN, vooral via interface	Meestal geen volledige toegang tot de code. Daarentegen juist in het algemeen vaak veel en gepubliceerde validatietesten en uitgebreide documentatie.	Bij een buitenlands model zullen hier kosten aan verbonden zijn en is de mate van aanpasbaarheid afhankelijk van de bereidwilligheid van de model eigenaar.	Voor complexere modellen, vaak alleen toegang via interface. Inhoudelijke ondersteuning tegen betaling	Zijn veel voorbeelden van. Vergt goede contracten.	Minder controle over regelmatig onderhoud. Controle over updates betekent kosten. Vanuit Licenties kan onderhoud worden bekostigd, ZIN kan dit afspreken.
Geen duidelijke eigenaar (open source model)	Geheel afhankelijk van modelstructuur	Code is volledig toegankelijk, niet per definitie altijd heel duidelijk of uitgebreid gevalideerd.	Alleen mits het model ontwikkeld is voor Nederlandse setting of voldoende flexibel is. Aan de model-gebruiker om dit te regelen.	Toegang meestal via platforms. Geen inhoudelijke ondersteuning	Kan risico zijn voor data-eigenaren. Niet voor modelresultaten, omdat model meestal voor eigen gebruik is te downloaden.	Eventueel problematisch. Het is aan de gebruiker om dit te doen indien nodig.

Business case	Flexibiliteit	Transparantie & Validatie	Toepasbaarheid in Nederlandse situatie	Toegang en gebruikersondersteuning	Toegankelijkheid en privacy	Updates en onderhoud
Coöperatief eigenaarschap	Afhankelijk van model en tijd en kennis bij onderzoeksgroep.	Toegang tot de code voor ZIN medewerkers, voor externe gebruikers niet. Gepubliceerde validatietesten en documentatie.	Hoogstwaarschijnlijk gebaseerd op Nederlandse data, omdat dit meestal een Nederlandse groep zal zijn. Voor internationale samenwerkingen is de aanpasbaarheid afhankelijk van de beschikbare middelen.	Waarschijnlijk aan de onderzoeksgroep om dit te regelen. Infrastructuur bestaat meestal. Interface oplossing ook mogelijk. Inhoudelijke ondersteuning aanwezig.	Vanwege betrokkenheid van ZIN mogelijk extra garantie voor dataeigenaren. Vergt goede contracten.	Controle over updates betekent kosten. Vanuit Licenties kan onderhoud worden bekostigt, ZIN kan dit afspreken.
Academisch eigenaarschap	Afhankelijk van model en tijd en kennis bij onderzoeksgroep.	Gepubliceerde validatietesten en documentatie met mogelijk veel draagvlak in verband met objectiviteit.	Hoogstwaarschijnlijk gebaseerd op Nederlandse data, omdat dit meestal een Nederlandse groep zal zijn.	Waarschijnlijk aan de onderzoeksgroep om dit te regelen. Infrastructuur bestaat meestal. Interface oplossing ook mogelijk. Inhoudelijke ondersteuning aanwezig.	Ook hiervan zijn voorbeelden. Vergt goede contracten.	Controle over updates betekent kosten. Vanuit licenties kan onderhoud worden bekostigt, ZIN heeft minder invloed.

1   Introduction and Background

The Dutch National Healthcare Institute has initiated the current project, to investigate disease models as a possible option to support more structured use of health economic evaluation and other applications of disease models as part of its policy advisory role.

Currently health economic evaluations and other simulation model outcomes play a role in reimbursement decisions concerning medicines with added value, but less so in reimbursement decisions on non-drug treatments, in guideline development, or in the program "Zinnige zorg" (which critically evaluates all healthcare interventions within a certain area of care, e.g. respiratory disorders, or mental health). Also, the initiative for model development rests with applicants for reimbursement, resulting in little consistency over different treatments for the same disorder.

The research team working with the Dutch Healthcare Institute on this project consists of the following researchers and institutions:
- Dutch National Institute for Public Health and the Environment (RIVM): Dr TL Feenstra, Dr GA De Wit; Dr A van Giessen; R Hoogenveen.
- University Medical Centre Utrecht: Dr GA de Wit; Dr GJW Frederix; Dr J Wang.
- University of Twente: Dr H Koffijberg; MSc X Pouwels
- Maastricht University Medical Centre+: Prof Dr M Joore; Dr B Ramaekers;
- Groningen University: Dr TL Feenstra

In addition, Prof Paul Tappenden (Professor of Health Economic Modelling, HEDS, ScHARR, University of Sheffield, Sheffield, UK), Dr Veerle Coupé (Associate Professor, Chair of the Decision Modelling Center, Amsterdam University Medical Centers) and Associate Professor Hossein Afzali (College of Medicine and Public Health, Flinders University, Australia) are involved as project advisors.

The project consisted of three tasks:
1. To build and provide access to an up-to-date disease model, by way of a model interface.
2. To investigate the methodological and organizational issues involved in using disease models for health care policy support.
3. To report on the findings.

The current report is the result of task 3.

1.1   Introduction

The Dutch Health Care Institute (Zorginstituut Nederland, ZIN) wishes for more information on and experience in using disease models as part of decision making regarding complex questions in health care policy, and more specifically concerning the management of the basic healthcare package. This concerns all policy decisions related to the contents of the mandatory part of the basic healthcare package. These are reimbursement decisions,

but it also concerns support in clinical guideline writing and the evaluations of current care as part of the "Appropriate Care" program. In the remainder, the intended use of disease models is with a general term referred to as "health care assessment".

The current use of health economic decision models by ZIN is mostly confined to the single use models that are submitted by the registration holder as part of pharmaco-economic assessments supporting reimbursement advice concerning new medicines. These pharmaco-economic assessments are cost-utility analyses of the new drug compared to the standard of care. In the Netherlands, other agencies further apply health economic decision models in support of policy making concerning management of infectious diseases, public health policy aiming at prevention through a healthy lifestyle and population screening programs, however that is outside the scope of the report.

A range of challenges arises both in the process of agenda setting and in the process of judging and using model-based pharmaco-economic evaluations. Table 2 lists these challenges, as identified by the team. Many relate to the conflicts of interest that arise since companies building and commissioning the models have financial incentives in getting a favourable outcome for the medicine under assessment. Others arise from the tension between applying model-based cost-effectiveness analyses, and performing a budgetary impact study or appropriate care evaluation separately.

A possible improvement of this situation may be for ZIN as the advisory agency to take more control in the model development process. Given the resources required for building a proper health economic decision model, this could for instance be achieved by applying the same disease model when a medicine relates to the same disorder as a previous assessment. This may be more efficient than building a new model for each assessment and has the added advantages of enhancing insight into these repeatedly applied models and their assumptions, as well as bring more consistency between the various assessments. Repeated applications of a disease model brings certain requirements for the models in question. Such disease models suitable for repeated use, that is, to evaluate different treatments for the same disorder, will be called multi-use disease models in the current report. See however also 2.2 on terminology, since the idea of a multi-use disease model and how it differs from single use models is not crystal clear yet. Many different names have been used to refer to similar concepts. The term "whole disease model" has been introduced for disease models with a broad scope allowing the evaluation of interventions over the entire course of disease [1], while others stressed the standardization aspect and used the term "reference models" [2, 3], and yet another often used term is "generic model". [4] As part of our project we therefore started with a further investigation of the definition and terminology.

Irrespective of the terminology, having more control over health economic decision models may also facilitate that model are more widely used than only in support of economic evaluations for reimbursement decisions. For instance, in budget impact analyses and in support of clinical guidelines and for appropriate care evaluations.

An element of a more extensive use of disease models and more active role for the HTA agency will be the evaluation of new treatments in relation to existing treatments. Their place in the treatment pathway has to be determined based on their effectiveness and cost-effectiveness compared to all existing treatments. Concerning the development of clinical guidelines, several treatments, or even all available treatments should have to be

evaluated simultaneously (this is sometimes called a multiple technology appraisal[5]). Multi-use disease models with sufficient width and depth may allow to perform such broader assessments. For budgetary impact analyses, model-based projections of disease burden and health care costs could be produced. This requires multi-use disease models to reflect properly the actual patient population in the setting of interest, that is, to incorporate the relevant demographic and epidemiologic information. It is also possible that multi-use models could support the optimization of treatment strategies that consist of multiple treatment lines or steps. This requires complete and proper modelling of all interconnections between these treatment lines. Clearly, the requirements to a multi-use disease model vary with their intended applications as well as with the disorder modelled. Hence, investigating issues related to the development and application of multi-use disease models seems the natural first step before their implementation in practice. In particular, the usefulness and applicability of multi-use disease models will be investigated for the purpose of "risk-based management of the basic package", involving on-demand reimbursement dossiers, as well as ZIN-initiated dossiers, condition wide treatment reviews, and clinical guideline development.

This report is part of a tendered project by ZIN, to support their possible future application of multi-use disease models in policy advice. The requirements as set out by ZIN were to illustrate with the help of a case-study (Diabetes Mellitus was chosen as topic by ZIN) how organizational and methodological issues met in developing and applying multi-use disease models could be solved. The report provides first a blueprint developed to enhance the generalizability and applicability of the findings of the case study, and ensure inclusion and description of all issues encountered during the development and application of multi-use disease models. After this, recommendations regarding these issues based on findings from the case study are discussed. While performed in commission by ZIN, in the remainder of the text we will use the term HTA agency as a more general referral to ZIN and similar agencies in Europe.

Alignment with other ongoing research projects commissioned by ZIN was sought. A multi-use disease model on prostate cancer is being developed, using the data of the Dutch CAPRI registry. This study focuses on data requirements and data-handling to support multi-use disease models, and provides as a case study an evaluation of the whole range of medications available for metastatic prostate cancer over different treatment lines. The project "Regie op registers voor dure geneesmiddelen" performed by ZIN on request of VWS investigates how existing disease registries are put to use in supporting management of the content of the reimbursement package. Like the latter project, the current project aims at supporting pro-active and agenda-setting policies, as well as policies that focus in a more integral way on disorders and their treatment, rather than policies based on reactive evaluation of single technologies.

1.2 Reading guide

Chapter 2 reports on the approach for and results of the blueprint study and covers the following topics: terminology, applications, organizational and methodological challenges associated with the development and application of multi-use disease models. Chapter 3 then builds on the study results, but takes a more policy oriented perspective to suggest five business cases relating to the implementation and application of multi-use disease models for an HTA agency. Furthermore, the benefits and limitations of introducing multi-

use disease models in support of risk-based management of the health care insurance package are discussed. Chapter 4 concerns the case study on diabetes and describes the model aim, structure and input data in general terms, to continue with lessons learned from the case study concerning the issues identified in chapter 2. A detailed user manual containing full model documentation will be delivered separately. Chapter 5 finishes with an overall discussion and policy recommendations.

Table 2 Overview of challenges encountered in current application of health economic decision models to support health care assessment.

Type of challenge	Summary of challenge	Further clarification
Organizational	Stakeholders involved late	Apart from selected clinicians involved in the model development, stakeholders may only comment to the draft assessment report as written by the HTA-agency.
	Conflict of Interest model developers	Model developers are commissioned and paid by the registration holder who has a clear financial stake in reimbursement.
	New process started for each medication/treatment.	When different medications have different registration holders, different models will be used, implying inefficiency and inconsistency.
	Not aligned with clinical guidelines	In clinical guideline development, economic evaluation plays a limited role and when used this is not aligned with reimbursement decisions.
	Role HTA-agency is reactive	The reimbursement process is organized in such a way that the HTA-agency is reviewing existing models, and can only ask for clarifications and improvements once.
Methodological	International setting	Most registration holders apply for reimbursement in many countries and re-use the same disease model, which often results in a model that is insufficiently adapted to Dutch situation.
	Model structure hard to adapt	The model developer did not consider flexibility regarding structural adaptations
	Oversimplified models	Disease models tend to be very specific and intended for single use, causing differences between evaluations that may be unwanted. This reflects a lack of resources, time and incentives at the side of the model developer, inherent in the current process.
	Limited uncertainty analysis and model validation	The uncertainty analysis and validation of the disease model tend to be too limited.
	Ignore interconnections between treatments.	Evaluations ignore knock-of impacts, that is, interconnections between treatments are ignored. For instance, if a medicine is added to first line treatment, this may impact the results of second and third line treatments.
	Disregarding or incorrectly modelling adverse events and comorbidities.	Lack of stakeholder involvement in an early stage of the modelling cycle may be partly responsible.
	Lack of transparency	Disease models are often not fully transparent, even when the source code is provided. For most HTA agencies, time to thoroughly review the model is limited.

2 Blueprint: approach and intermediate results

2.1 Introduction to methods for blueprint

To enable useful policy advice regarding the application of multi-use disease models, possible methodological and organizational issues for their proper application need to be clear and possible solutions for these issues should be investigated. The current chapter reports on this process and aims to provide a broad overview of methodological and organizational issues related to the application of multi-use disease models to support health care policy. This also involved assessing the characteristics, potential applications and criteria for a multi-use disease model.

Multi-use disease models are not just more complex versions of single use health economic decision models, since being suitable for multi-use implies a number of requirements. Also, the application of multi-use disease models brings organizational issues and calls for specific arrangements, for instance regarding licensing and access to model code. Therefore, a blueprint has been developed to: first, provide an overview of issues that could arise and second, discuss possible steps towards solutions for these issues.

In the past, several authors have addressed concepts related to multi-use disease modelling. Examples are "Whole disease models" as discussed by Tappenden[6] and "reference models" as discussed among others by Afzali et al. and Frederix et al.[3, 7, 8]. Other terms have been introduced previously, like Weinstein's "Policy Model" in CHD [9] and the "Treatment Pathways Models" (e.g. prostate cancer and atrial fibrillation in Lord's MAPGUIDE project [10]). Finally, "generic models" have been coined by Snyder et al.[4]

Tappenden et al. defined a "whole disease model" according to three principles: 1: The model boundary and breadth should capture all relevant aspects of the disease and its treatment—from preclinical disease through to death; 2: The model should be developed such that the decision node is conceptually transferable across the model; 3: The costs and consequences of service elements should be structurally related. The application of these general principles allows for the health economic evaluation of interventions for prevention, diagnosis and treatment across the whole disease pathway using a single mathematical model. Afzali et al.[2] defined "reference model", or "disease specific reference model" as a model that should represent "the knowledge and uncertainty about states/events relating to the disease progression on the basis of the best available evidence." It is to be applied to a wide set of interventions for a specific disease (e.g., drugs and procedures that may target alternative mechanisms or stages of disease).

Next to this, the development of open source models is relevant in the context of multi-use disease models.[11-14] In principle, both single use or multi-use models could be made open source. This will serve the purpose of transparency and accountability. However, next to this, an important principle of open source is that the models will be open to others, not just for review, but also to apply or even to adapt. So called "modelling frameworks" or "empty shell models" are the most prominent

published open source models, but these are not yet complete health economic decision models.[14-18] They facilitate the development of health economic decision models by offering ready-made modelling code, that can be filled by the model developers with their own input data to produce an application in a certain disease area. Hence, the frameworks are general and do not contain any specific input data or parameter estimates. Such frameworks do not classify as multi-use models, since before they can be applied to a certain decision problem, a lot of effort has still to be spent on incorporating all relevant input data, obtaining parameter estimates, and on running and validating the model. Still they can be very useful as starting points for building a multi-use disease model. Finally, in several fields outside reimbursement decisions, for instance in the field of public health modelling, multi-use has been the standard. These models are not multi-use disease models, since a typical public health model covers several diseases. Not all of them include economic outcomes. Examples are the RIVM Chronic Disease model[19], the Prevent model[20], the PopMod model[21], the DYNAMO-HIA model[18], the ECONda tool[17] and the UKHF microsimulation model[17]. From these public health models several important lessons concerning maintenance, organization of access and validation can be learnt for multi-use disease models.

While a lot of work has been done, approaches seem either very ambitious (whole disease modelling), or of limited direct applicability (empty frameworks, disease specific reference models), and many different terms have been used, with also varying definitions. Also, the use of these models in policy support has been limited. Hence the aim of the current study is to develop a blueprint that supports practical application of multi-use models for health care assessment.

2.2 Terminology and definition

The overview of concepts above highlights that terminology varies considerably and is not crystal clear. For the remainder of this report we choose the term multi-use disease model, defined as:

"A health economic decision model that properly represents (part of) the dynamics of a disease trajectory to accommodate the evaluation of a range of alternative health technologies for the management of this disease. When several disease stages are included, consistent comparisons over these stages are possible."

This goes along with a list of criteria that further specify requirements for specific applications, see section 3.3.1 below.

The current definition is based on our panel survey results (see 2.4.2) , as well as advisory board comments, and discussion within the team and with ZIN.

2.2.1 *Examples of multi-use disease models*

To further illustrate the concept of a multi-use disease model, some examples are described here.

As a first example, diabetes models are discussed. Diabetes is a complex disorder to model, because it has many complications, both microvascular and macrovascular, and its incidence and progression is affected by a range of risk factors. Currently, several diabetes models exist internationally, which could be classified as multi-use disease models, although several of them would not satisfy the criterion of

enabling projections of policy scenarios. Examples of diabetes models that have been applied in several settings and for various interventions are the CDC Diabetes model[22-24]; the ECHOT2 Diabetes model,[25] the UKPDS-OM [26] and the IQVIA Core Diabetes model.[27] The Sheffield Diabetes model,[28] and the BRAVO model are the most recently developed examples.

Diabetes modelling groups have initiated a cross validation network, to improve the validation status of their models and exchange expertise.[29] Interestingly, many of these models use the same set of risk prediction models as the core of their model, as well as sources for quality of life values for various disease states.[30] The models have been applied to a wide range of interventions, most often as part of economic evaluation studies (cost-effectiveness studies), to support reimbursement decisions for new medications, or to support government prevention policies.[32-34] Next to that, the models were used to perform budget impact analyses and a resource optimization study [31]. Projections with Diabetes multi-use models have also been published, and compared to other types of projections. Finally, the UK clinical guidelines for treatment of Type 2 Diabetes in adults include an extensive appendix on the economic aspects of medication treatment, addressing treatment steps. These analyses were performed with an adapted version of the UKPDS-OM.[35]

Another area where multi-use models have been applied extensively is the support of cancer screening programs. To evaluate a cancer screening program requires again a rather complex and resource intensive modelling effort. Reviews of screening models in the areas of breast cancer,[36] colon cancer,[37] and cervical cancer indicate the existence of a limited number of repeatedly used models. The models have been applied to support population screening policy, both with epidemiological projections and with economic evaluations. Recent work has also applied optimization to find the most efficient screening frequency. Results are for instance found in guidelines for screening.[38, 39]

As we have illustrated by these example disease areas, multi-use disease models have been in use for decades, especially for those disease areas where health economic decision models are necessarily complex and require substantial efforts to build them. They have been applied both for typical cost-effectiveness studies to support reimbursement decisions, but also often to support policy decisions by public health authorities, and as part of the development of clinical guidelines.

2.3 Methods for blueprint

2.3.1 *General approach: expert panel and team discussions*

To answer questions about the conditions for multi-use disease models to be suitable for supporting decision making, an expert panel was approached in two survey rounds. These rounds had a Delphi-like structure, in that responses from round 1 were fed back to the panel in round 2. Adding to the panel responses, team discussions within the consortium served to process the panel results. Adding to these team discussions, the viewpoints from the Dutch Healthcare Institute were sought by organizing meetings and comment rounds. Finally a draft of this report was elaborately commented upon by our scientific advisors.

The following aspects were each addressed:
— The proper definition and terminology;
— The potential applications of a multi-use disease model; and
— The process of developing a multi-use disease model and the issues (both organizational, legal, methodological and technical) that have to be addressed when developing and applying multi-use disease models; The panel surveys were designed to address these aspects.

Expert panel
Purposive sampling was used to recruit an expert panel comprised of experts from academia, pharmaceutical industry, consultancy firms, or with a governmental background. A list of experts eligible as participants in the surveys was developed by members of the study team, and 110 experts were included in the expert pool and contacted by one of the team members. The Expert panel was engaged in two survey rounds, with the second round serving to comment on results from the first, asking for confirmation and priority setting. This served to generate consensus on terminology and definition and to prioritize potential applications and issues to be addressed.

Team discussions
After each survey round, answers were extracted by team members, and results were presented to all team members and to colleagues from the Dutch Healthcare Institute. Opinions from the expert panel, expertise from the team and input from the Dutch Healthcare Institute were all combined in these team discussions. Additionally, the results of the first survey round were presented twice to an international audience and discussed with them. When deemed necessary, additional scoping reviews were performed for specific methodological aspects and additional expertise/good practice experience was sought for specific organizational aspects.

2.3.2   *Round 1*
The first round of the expert panel survey concentrated on terminology, definition and generating an inventory of possible issues and challenges met when working with multi-use disease models. No ranking or scoring was elicited from the panel in this stage. The survey consisted of four topics. The full survey is found in Supplement 2.
Topic 1 concerned Terminology and definition. We asked survey participants to comment upon a proposed definition and discussed the proper term. Topic 2 concerned the elements considered essential to characterize a multi-use disease model. Respondents were asked to identify elements that they considered most important. Topic 3 concerned applications for multi-use disease models, asking the panel members to append and comment a list of possible applications for multi-use disease models. In Topic 4 of the panel document respondents were asked to list and discuss issues expected when implementing and using multi-use disease models for support of healthcare policy making. A list of potential issues was provided and comments and additional issues were solicited.
Topics 1 to 3 were processed by the team members by systematically summarizing all panel responses and representing them graphically where possible, so they could be fed back to the panel in round 2. For

Topic 4, all responses were coded by two team members independently, who then drafted a list of issues which was double checked and discussed by a third and fourth team member. This led to a draft gross list of potential issues, sorted into categories, based on similarity of topics. This list was then resorted and condensed during a consensus meeting of the research team. The team removed items that could be considered a general issue in HE decision modelling, or recommendations that would hold for all HE decision models. We tried to err on the conservative side, keeping issues rather than removing them. Finally, in a new table, the team reduced the number of items in the table by skipping recommendations and items that we consider to be irrelevant within the setting of our study aim, i.e. to support an HTA agency in the application of multi-use disease models for health care assessment (intended to support reimbursement decisions, clinical guideline writing, and evaluations of current care).

Based on the findings from the first round and feedback from the Zorginstituut on these findings, a second round was developed.

2.3.3 Round 2

In round 2, participants were provided with a summary of round 1, and asked to provide their comments and priorities. The survey was organized in 5 questions, with the possibility for responders to provide with additional comments.

Question 1 again was about the terminology. The 9 alternatives (7 from the panel + 2 more resulting from discussions after presentations of the results of round 1) provided for "disease specific model" were shown to the participants. Based on the input from round 1, the team proposed the term "Multi-use disease model" and comments were asked for.

Question 2 was about the definition. We asked survey participants to comment upon the revised definition of a "Multi-use disease model" as follows: "A health economic decision model that properly represents the length and dynamics of a disease trajectory to accommodate the evaluation of a range of current and future health care interventions. It enables projections of policy scenarios, based on setting specific epidemiological parameters. When several disease stages are included, consistent comparisons over these stages are possible. This enables its repeated use, possibly after adaptations, for health economic evaluations and to support evidence based health care policy regarding a certain condition."

Question 3 was focused on the suitable applications of "Multi-use disease model", and participants were asked to select a maximum of 5 most important applications from a list of 10 possible applications (Table 3 below) and rank them in order of importance (from 1 to 5, with 5 indicating highest priority).

Table 3 Potential applications for multi-use disease models, as presented to the panel for ranking

Application (similar applications were combined)
Resource allocation: Optimization of resources over a set of interrelated interventions over the entire disease pathway of interest.
Budget impact estimation: estimation of the overall costs (and health benefits) of certain policy choices for a jurisdiction, within a certain year/range of years.
Guideline development: support evidence over the costs and benefits of several interventions in a consistent way
Projections: provide insight in the expected numbers of patients over time.
Compare alternative policies concerning prevention and treatment
Exploration: new treatment options/scenario analysis/subgroups (e.g. by SES)/biological mechanisms
Support government investment decisions
Identification of key uncertainties and their potential impact
Equity analyses: You may want to study the effect of different interventions in people with e.g. various economic status
Umbrella trials (network meta-analysis type of use)

For Question 4, a list of 32 issues proposed in a consensus meeting by the team based on the first panel survey round was provided to the panel (Table 4), and participants were asked to score items in the new table for relevance and feasibility. To reduce the workload for each panel member, each panel member only had to score a set of 7 issues out of these 32 issues. A total of 70 points could be distributed to 7 issues presented in the question.

For Question 5, a list of solutions/recommendations as raised by panel members in the first round was provided to the panel, and participants were asked to give their opinion on the acceptability (highly desirable, acceptable, unacceptable) of these solutions/recommendations (Table 5). Again, to reduce the workload, each panel member only had to answer 5 questions out of 20.

Table 4 Complete list of issues, as suggested by the panel in round 1 and grouped by the team

Category	Issue/challenge/choice to be made
Organization (access & ownership)	1. Funding for maintenance
	2. Funding for hosting / Q&A to support users
	3. Ownership (model and results)
	4. Role of stakeholders
	5. Mandatory or optional use in policy contexts
	• What kind of software is allowed or suitable (in relationship to accessibility/users/regulation)
	7. Liability agreement for wrong results (caused by wrong model)
	8. Prevent misuse (uniformed, inappropriate),
	9. Licensing + how to organize this
	10. How to ensure collaboration (synergy) between different research groups/ stakeholders
	11. Confidentiality agreement (e.g. a company using it on a drug in development)
Development of model	12. Consider a modular approach
	13. Model complexity/depth/degree of detail (balance specificity and generality)
	14. Should a multi-use model be an empty shell or a setting specific model
	15. Funding for development
	16. How to ensure sufficient transparency of model structure, assumptions and input data.
Input data.	17. To find an acceptable solution to the tension transparency & replicability versus privacy patient level data.
	18. When model is used repeatedly, and is based on patient level data, how is model use compatible with GPRD.
Validation and transparency	19. Communicating model limitations
	20. Risk in using one model structure; blinder for structural uncertainty;
	21. Comparability with other models or model outcomes
Model use.	22. Transferability (what part of a model is to be based on setting specific data?)
	23. How to ensure access to models for potential users., more practically
	24. Limits to acceptable run-time/software
Model results	25. Organize governance for access to model results of certain applications.
	26. How to improve model understanding (face validity, explanation)
Model maintenance (technical)	27. Should there be an 'official' (updated) version.
	28. How to have a sustainable knowledge base (expertise sits in humans) on the model including transparent documentation
	29. Ensure sufficient adaptability
	30. Time required to get approval for adaptations of the model
	31. Way of updating evidence that does not require adjustment of model structure (user interface)
	32. Way of updating evidence that would require adjustment of model structure

Table 5 Complete list of recommendations as suggested by the panel in round 1

Category	Recommendation
Organization (access & ownership) Money, legal, IP, etc.	1. Ensure future access by having models maintained by a public authority.
	2. Ensure independent owner, e.g. a public authority (independent of academic centers)
	3. Have free access
	4. Have licensed access
	5. Have a registry of models - to help identifying models
Development of model	6. Accommodate for regular updates (e.g. based on automated links to registries/claims data)
	7. Ensure interdependencies between decisions at different stages of a disease
	8. Make a deliberate choice where to start, e.g. at the healthy population or not.
	9. Do include the healthy population
	10. Do not include the healthy population
	11. Include subgroups/heterogeneity
Input data	12. Should be transparent. (FAIR)
	13. Has to represent trends over time
Validation and transparency	14. Use very strong validation requirements
	15. Perform revalidation after updates
Model use	16. Ensure an accessible interface
	17. Ensure freedom to users to adjust the model to their own requirements and/or data
	18. A model should only be used by the developers
Model results	19. Ensure proper storage of results. For archiving of research results.
Model maintenance (technical)	20. Have regular updates + version control

2.3.4 *Priority setting*

Topics from Table 4 as presented to the panel in round 2, were also prioritized by the team based on the following 3 criteria: 1) need for further research; 2) policy relevance/need for policy decision; 3) acceptability of policy decision/expected differences among stakeholders. This prioritization drove the approach for each topic/issue, with a choice being made, to gather additional literature, to seek more expert input, to discuss with the Dutch Healthcare Institute and other stakeholders, and/or to find best practice example solutions. Priority setting was also discussed with the Dutch Healthcare Institute and priorities from the expert panel were compared with the outcomes of these discussions. In a next step, the team re-organized the topics, combining related topics and re-ordering issues in such a way that a logical discussion would be possible. This discussion as much as possible took all issues into account, while more effort was put into those issues that were prioritized by the panel and/or the Dutch Healthcare Institute.

2.4 Results from panel surveys

2.4.1 *Round 1*

In Round 1, a total of 102 questionnaires were sent out, and after sending two reminder emails, 51 responses were received. The response

rate for Round 1 was 50% (51/102). Relatively little answers were obtained from people working directly in industry, while people from academia, consultancy (these work for industry mostly), and policy were all represented, see also Supplement 1.

The results from round 1 are summarized in detail in Supplement 2. A brief summary is provided here. The panel mentioned a variety of alternatives for our first proposal for terminology, which was "disease specific model", two more alternatives were proposed by presentation audiences. Based on all suggested alternatives, we chose the term "multi-use disease model" and included that in the second panel survey for approval. The panel also commented on our definition, suggesting smaller or larger edits. We summarized all proposed changes, and drafted a new definition, which we again submitted to the panel in the second survey round. Panel scores for the characteristics of a multi-use disease model are shown below (Figure 1). Regarding applications, the panel commented on and added applications, as shown in Table 6 below. Finally, a broad range of issues was submitted and discussed, which resulted in a table with issues (Table 4) and a table with suggestions to address some of these issues (Table 5).

Looking at this graph, two elements are considered important by many respondents, namely covering a wide range of interventions and being suitable for repeated use. Two further elements were considered important by more than half of those who answered to this question, being able to produce policy projections, and estimates that are consistent over different disease stages. Based on these results, the use of the term "multi-use", and the elements of projections and the inclusion of a wide range of interventions in our definition and terminology is supported by the panel. Note however that a wide range of interventions does not necessarily imply that a large part of the disease course needs to be covered, although often this will be the case

Table 6 below lists our applications followed by the new applications mentioned by the panel, as well as whether or not these would be relevant for an HTA agency in its consideration of applying multi-use disease models for health care assessment intended to support reimbursement decisions, clinical guideline writing, and evaluations of current care (team's opinion). Applications that the team considered as already covered or not feasible (even with a huge amount of resources to build the model) were removed from the list of new applications.

Table 4 above contains new issues raised by the panel in round 1, as well as issues already listed in the panel document, after combining them into categories as discussed during a team meeting. Table 5 presents recommendations as expressed by the panel members in round 1. Recommendations strongly varied in degree of concreteness, and issues in level of detail. Whenever possible, we combined them. Clearly opposing recommendations were put next to each other.
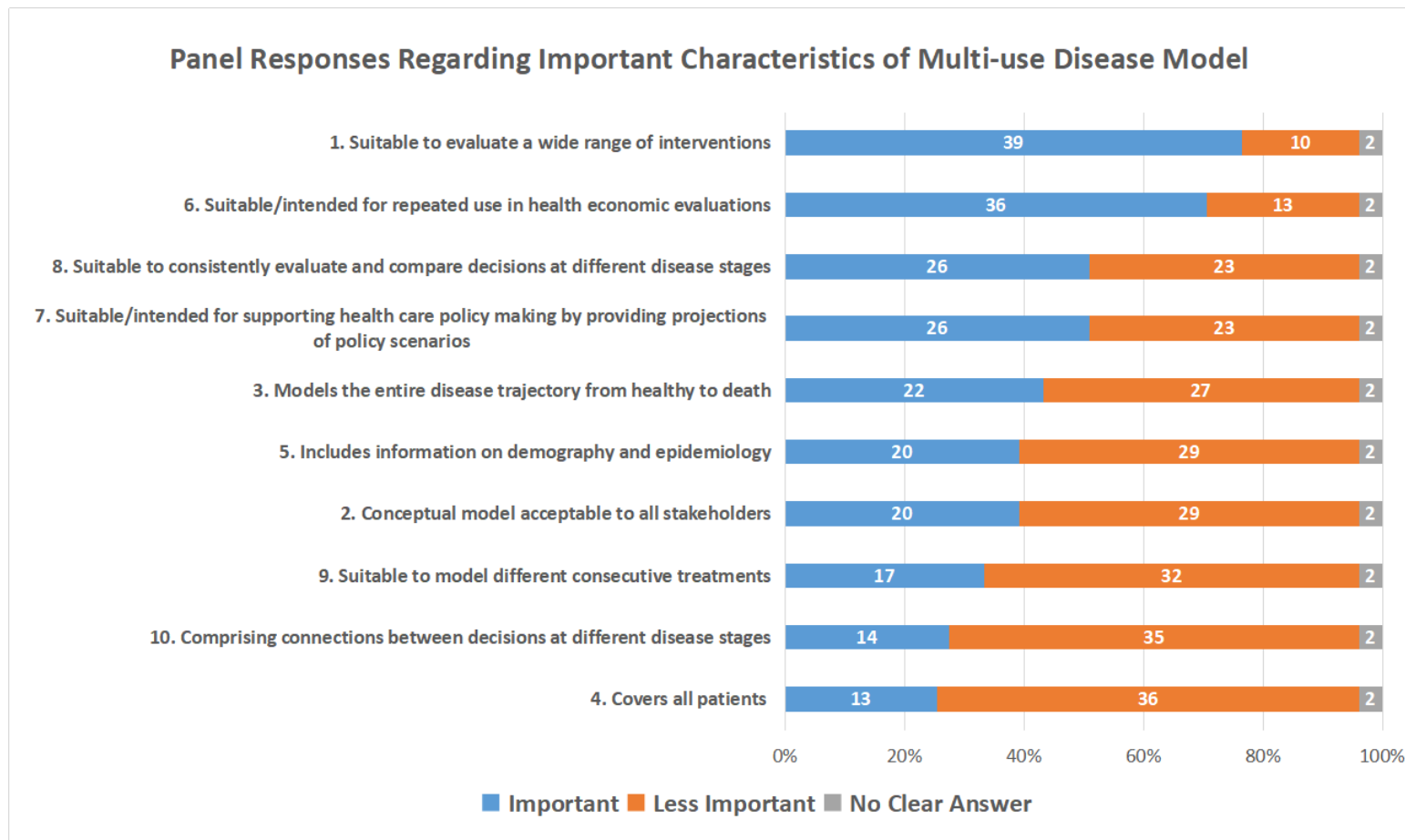
Figure 1 Panel scores regarding multi-use model characteristics, ordered by number of respondents scoring a characteristic as important. Round 1

Table 6 Applications for multi-use disease models, as listed by the panel, and judged by the project team for relevance.

Application (similar applications were combined)	Relevant for purpose of HTA-agency (e.g. Dutch Healthcare Institute)
Resource allocation: Optimization of resources over a set of interrelated interventions over the entire disease pathway of interest.	Possibly
Budget impact estimation: estimation of the overall costs (and health benefits) of certain policy choices for a jurisdiction, within a certain year/range of years.	Yes
Guideline development: support evidence over the costs and benefits of several interventions in a consistent way	Possibly
Projections: provide insight in the expected numbers of patients over time.	Possibly
Compare alternative policies concerning prevention and treatment	Yes
Educational or training purposes	No
Exploration: new treatment options/scenario analysis/subgroups (e.g. by SES)/biological mechanisms	Possibly
Support decisions by insurance companies	No
Support government investment decisions	Possibly
Assist in trial design and research prioritization.	No
Identification of key uncertainties and their potential impact	Possibly
Foresee (future resource use and) capacity limitations	No
Drug/device development decisions and R&D for industry, for (innovative and expensive) drugs	No
Individual prognosis	No
Equity analyses: You may want to study the effect of different interventions in people with e.g. various economic status	Possibly
Clinical trial simulation, synthetic control arms	No
Umbrella trials (network meta-analysis type of use)	Possibly

2.4.2 Round 2

In Round 2, a total of 61 questionnaires were sent out, since we did not approach persons who in round 1 were clearly not willing or able to respond. After sending two reminder emails, 42 responses were received (69%). See also Supplement 1.

Terminology
The term "multi-use disease model" was approved by a large majority (35/42, 83%) of the responders. For those who disagreed (7/42, 17%), the concerns were mainly focused on the word "multi-use". It was brought forward that "multi-use" itself might be confusing, since it can refer to several "multi" things, e.g. times, purposes, diseases, treatments, countries.

Definition
The definition as proposed in survey Round 2 was approved by most (35/42, 83%) panel members.
A Multi-use disease model is "A health economic decision model that properly represents the length and dynamics of a disease trajectory to accommodate the evaluation of a range of current and future health care interventions. It enables projections of policy scenarios, based on

setting specific epidemiological parameters. When several disease stages are included, consistent comparisons over these stages are possible. This enables its repeated use, possibly after adaptations, for health economic evaluations and to support evidence based health care policy regarding a certain condition."

Potential applications of multi-use disease models
Regarding potential applications of disease models, Table 6 presents results after the first round and Figure 3 presents priorities based on the second round. The top two potential applications are comparing alternative policies and supporting resource allocation decisions, which received average scores around 2.5.
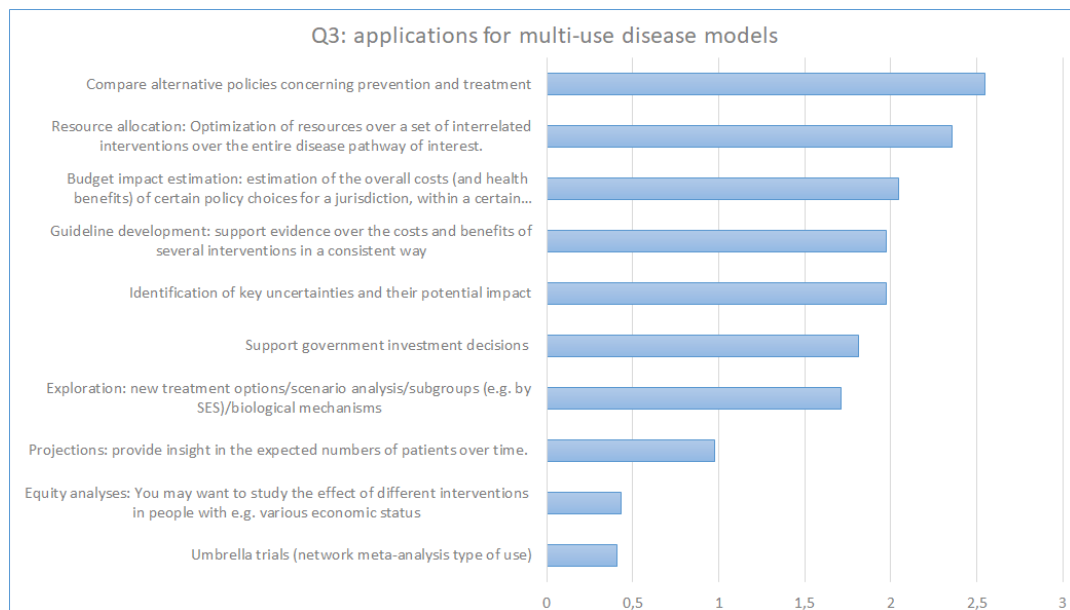
Figure 3 Applications for multi-use disease models along with their ranks

Three further potential applications had average scores around 2: budget impact estimation, guideline development, and identification of key uncertainties and their potential impact. On the bottom end, equity analyses and umbrella trials were rated as less relevant applications of multi-use models.

Issues to be solved with multi-use disease models
All issues were scored by at least 8 panel members (see Supplement 2). Issues receiving an average score above 10 were considered as important (see Figure 4 below). They are listed below:
- Q3. Ownership
- Q4. Role of stakeholders
- Q10. How to ensure collaboration (synergy) between different research groups/ stakeholders
- Q13. Model complexity/depth/degree of detail/balance specificity and generality
- Q15. Funding for development
- Q16. How to ensure sufficient transparency of model structure, assumptions and input data.

- Q17. To find an acceptable solution to the tension transparency & replicability versus privacy patient level data.
- Q20. Risk in using one model structure; blinder for structural uncertainty
- Q22. Transferability/what part of a model is to be based on setting specific data?
- Q23. How to ensure access to models for potential users., more practically
- Q26. How to improve model understanding/face validity, explanation
- Q27. Need for an 'official' (updated) version.
- Q28. How to have a sustainable knowledge base (expertise sits in humans) on the model including transparent documentation
- Q29. Ensure sufficient adaptability
- Q32. Way of updating evidence that would require adjustment of model structure.

These and other issues are discussed further in sections 2.3.4 and 3.1.
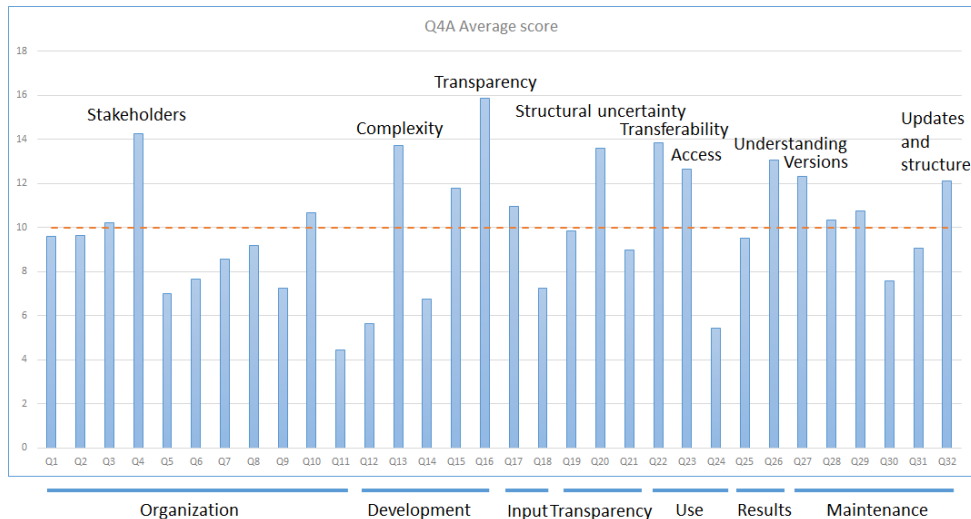
Figure 2 Average score of issues for multi-use disease models (round 2 expert panel)

Solutions to the issues/recommendations for multi-use disease models. Scores on recommendations presented in round 2 are summarized in Figure 5. Clearly, the experts would not advise to have a model only be applied by its developers, and to not include the healthy population. The latter is a bit hard to interpret. Licensed access received less support than free access. Large support (≥50% scoring highly desirable) was expressed for regular updates (>80%), proper storage of results, revalidation after updates (>80%), strong validation requirements, including time trends in multi-use disease models, FAIR/transparent modelling, including subgroups & heterogeneity, include the healthy population, accommodate regular updates, free access, and independent model owners.
From this it can be concluded that the expert panel in their definition of "multi-use disease models' tended towards more extensive models (including healthy population, strong validation requirements, regular updates, FAIR), and public ownership.
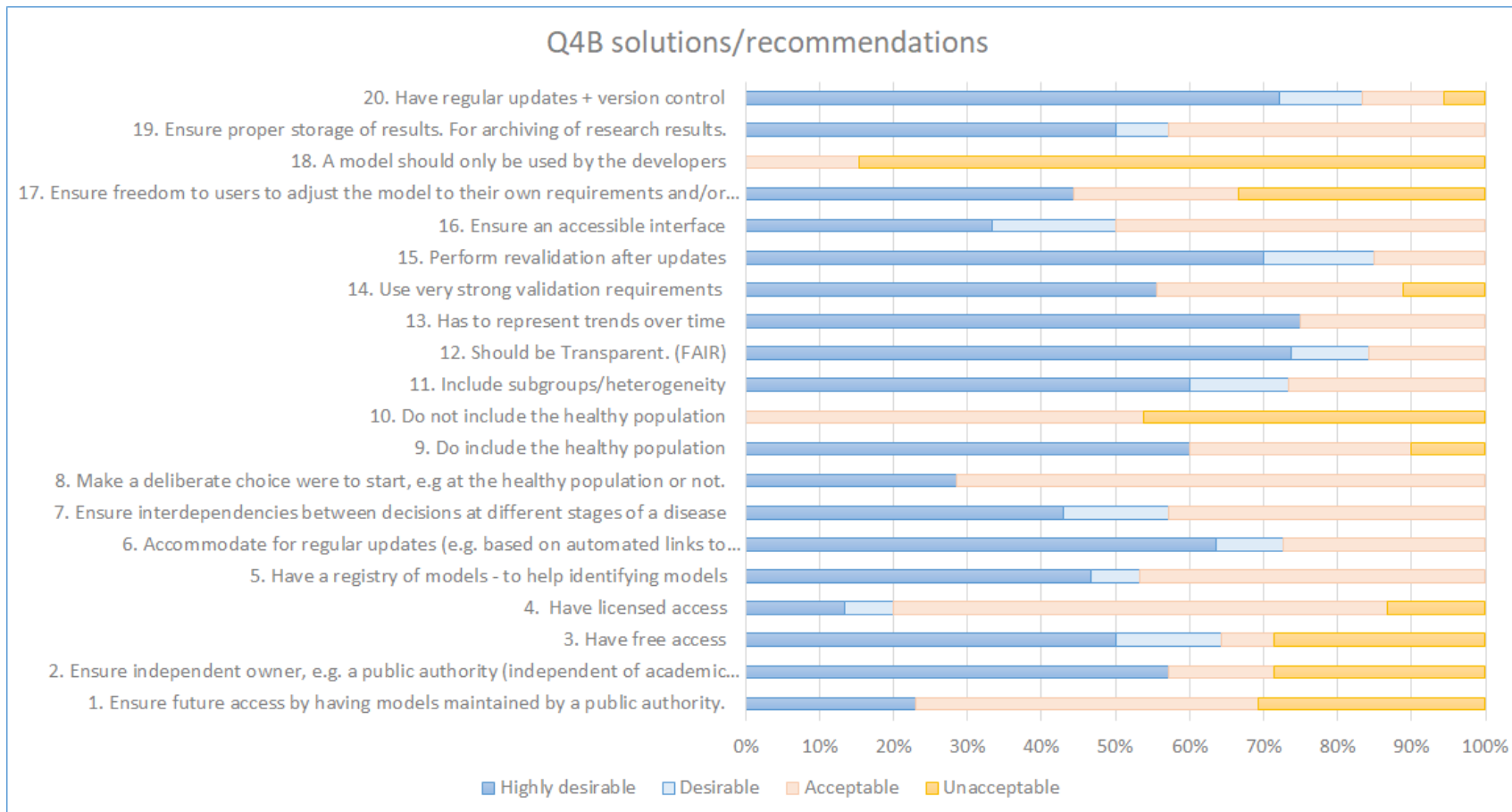
Figure 5 Panel scores for recommendations on applying multi-use models, panel round 2.

2.4.3 Further prioritization

The separate prioritization by the members of the Dutch Healthcare Institute mostly confirmed the priorities as selected by the panel.(Figure 4) After re-ordering and combining the topics, dividing them into organizational and methodological issues, a new list of topics resulted, as depicted in Table 7 below.

Table 7 Overview of issues and re-arrangements made by the team, priorities indicated in orange.

Category	Issue in panel survey with its original numbering (see Table 4)	NEW STRUCTURE of TOPICS
Organi-zation (access & owner-ship)	3. Ownership (model and results)	Overarching topic
	5. Mandatory or optional use in policy contexts	Topic 1: Mandatory use
	1. Funding for maintenance	Topic 2: Funding for development, maintenance and hosting
	2. Funding for hosting / Q&A to support users	
	15. Funding for development	
	7. Liability agreement for wrong results (caused by wrong model)	Topic 3: Liability and prevention of misuse
	8. Prevent misuse (uniformed, inappropriate),	
	9. Licensing + how to organize this	
	4. Role of stakeholders	Topic 4: Stakeholders role and collaboration
	10. How to ensure collaboration (synergy) between different research groups/ stakeholders	
	6. What kind of software is allowed or suitable (in relationship to accessibility/users/regulation)	Topic 5: Software requirements
	11. Confidentiality agreement (e.g. a company using it on a drug in development)	Topic 6: Confidentiality
Develop ment of model	12. Consider a modular approach	Topic 7: Modular approach
	13. Model complexity/depth/degree of detail (balance specificity and generality)	Topic 8: Model complexity
	14. Should a multi-use model be an empty shell or a setting specific model	Topic 9: The role of empty shell models
Input data.	17. To find an acceptable solution to the tension transparency & replicability versus privacy patient level data.	Topic 10: Access to patient level data
	18. When model is used repeatedly, and is based on patient level data, how is model use compatible with GPRD.	Topic 11: Compatibility with GPRD
Valida-tion and transpa-rency	19. Communicating model limitations	Topic 12: Uncertainty analysis, Model validation and Transparency
	16. How to ensure sufficient transparency of model structure, assumptions and input data.	
	20. Risk in using one model structure; blinder for structural uncertainty;	
	21. Comparability with other models or model outcomes	
Model use.	22. Transferability (what part of a model is to be based on setting specific data?)	Topic 13: Transferability
	23. How to ensure access to models for potential users, more practically	Topic 14: Access for users
	24. Limits to acceptable run-time/software	Topic 15: Acceptable run-time
Model results	25. Organize governance for access to model results of certain applications.	Topic 16: Governance for access to model results
	26. How to improve model understanding (face validity, explanation)	Topic 17: Improve model understanding
Model mainte-nance (techni-cal)	27. Should there be an 'official' (updated) version.	Topic 18: Need for official updates
	28. How to have a sustainable knowledge base (expertise sits in humans) on the model including transparent documentation	Topic 19: Sustainable knowledge base
	29. Ensure sufficient adaptability	Topic 20: Adaptability of model and approval of adaptations
	30. Time required to get approval for adaptations of the model	
	31. Way of updating evidence that does not require adjustment of model structure (user interface)	
	32. Way of updating evidence that would require adjustment of model structure	

3 Blueprint, discussion of topics and introduction of business cases

3.1 Discussion of topics and their relation to business cases

This section describes each of the topics listed in Table 7 above and introduces 5 business cases for different choices regarding ownership.

3.1.1 *Organization: ownership, business cases, and implications*

The relevance of the requirements discussed in this section depends partly on the intended use of the multi-use disease models. Multi-use models have a range of potential applications, see also section 3.3.2. For the discussion below, the main application kept in mind was the use in support of reimbursement decisions by healthcare authorities. Ownership influences most other organizational issues, therefore five business cases of ownership are described in the current section. Next, the following topics that link to different ownership choices are described in section 3.1.2, 1) mandatory use, 2) funding for maintenance and hosting, 3) liability and prevention of misuse. Other organizational aspects are not directly related to ownership but are essential organizational aspects when developing multi-use disease models, and these are discussed in section 3.1.3. These are 4) stakeholders role and collaboration, 5) software requirements and 6) confidentiality.

Choices with regard to ownership influence the other organizational topics and should therefore be discussed upfront, model ownership often goes hand in hand with responsibility of model outcomes. To clarify this, five ownership options were distinguished and will be discussed further as five business cases:

A. Full HTA agency ownership
B. Private/Commercial ownership
C. Open source model (No single distinct owner)
D. Academic cooperation scenario (HTA agency+ research group)[1]
E. Academic or other research institution is owner.

Current multi-use disease models are in general owned by research groups and commercial organizations such as consultancy firms, so use either business case B or E. Several examples of open source models do exist as well (section 2.2.1 above). Financial consequences are directly linked to ownership structures and organizational choices.

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[1] Next to academic groups, other research institutes develop HE decision models. In the text below, when academic group is mentioned, this should be read broader as any not for-profit research institution
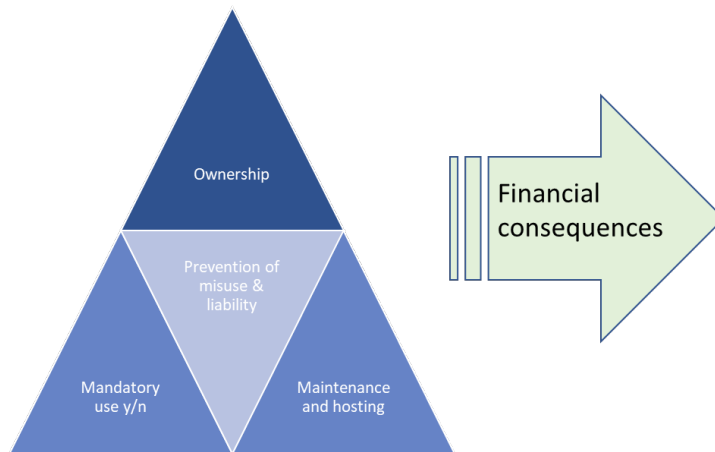
Figure 6 Three organizational aspects closely related to choice regarding ownership

3.1.2   *Organization: topics directly related to ownership*
         Topic 1: Mandatory use
Requiring mandatory use of a multi-use disease model influences other organizational factors such as ownership, liability, misuse prevention, licensing and confidentiality. For reimbursement decisions, the only authority who is able to require mandatory use is the HTA-agency responsible for assessment and appraisal, in the Netherlands, the Dutch Health Care Institute (ZIN). For other applications of multi-use disease models, mandatory use could be required by the organization responsible for the applications, for instance clinical guideline issuing bodies (in the Netherlands supported by ZIN) and (local) governments.

Currently, the use of multi-use disease models is in general not mandatory. Their use is related to stakeholders' trust in these models and their acceptance by health care authorities as reliable and valid models. Models widely accepted by industry and decision makers could be considered to be de facto mandatory. A clear disadvantage of this is that newly developed competing models may be more difficult to implement or decisions based on other models could be questioned due to this de facto mandatory model use. Hence a good procedure is required to validate and revalidate multi-use disease models and to ensure openness to improvements.
Also mandatory use could be implemented either very stringent, by requiring only the selected model to be applied in applications, or less stringent, by requiring that in applications, at least the selected model should be used, but leaving open the possibility to apply alternative models as well.

It seems likely that adoption of multi-use disease models without mandatory use takes a long time. Models should be accepted by all stakeholders, having proven their validity and flexibility to adaptations. Instead of requiring mandatory use, the HTA-agency could accept and support certain models. This might increase the speed of uptake of the model by end-users.

A risk of mandatory use that has been pointed out by some expert panel members is a lack of cross validation possibilities when for certain disease areas only few models are left as the multi-use models of preference.

A.   Full HTA agency ownership
Requiring use of a specific model for reimbursement decision is most straightforward for models fully owned by the HTA-agency. This does however raise questions whether it is desirable for the HTA-agency to charge fees for model use if model use is obligatory for reimbursement decisions.

B.   Private/Commercial ownership
If the model is owned by a third party mandatory use is difficult, as a third party should be paid for use of the model. This implies that the HTA-agency increases the work load and income of certain developers which could limit fair competition and might even be considered illegal state aid.

C.   Open source model (No single distinct owner)
The difficulty in requiring mandatory use of open source models for reimbursement decisions is the lack of insight regarding use and modifications of the model. This could result in unreliable model results and the use of outdated models since no one feels obligated to update and/or validate the models.

D.   Academic cooperation scenario (HTA agency+academic groups)
Ownership by a research institution together with the HTA-agency allows for external financing (i.e. licensing) as well as solves issues surrounding updating and validating of models. Questions remain whether possible issues surrounding fair competition between model suppliers will be adequately resolved under this scenario.

E.   Academic or other research institute ownership
Like with commercial ownership, mandatory use is somewhat difficult and could be perceived as unfair towards other groups. However, examples exist of models which have received preference by government agencies. See for instance the UKPDS-OM and NICE, and the MISCAN cancer screening models and the NIH.

Topic 2: Funding for development, maintenance and hosting
Funding for development is directly linked to ownership, since most logically the model owner will have to fund its development in the first place. Quite often this funding would come from a third party, that is models could be developed further initiated by questions from third parties with an interest in specific model applications.
Funding for maintenance and hosting depends on the expected lifetime and required updates of the model. However, even without specific adaptations of the model or its input data, a minimal level of maintenance is required to ensure that the model will run with updates of the software or operating system. If use of the model is mandatory for reimbursement decisions it would be logical that funding for maintenance will be provided by the authority claiming the mandatory use of the model, though one might argue that money saved from not

having to develop a new model can partly be paid in the form of licenses. We are not aware of any model maintained and hosted by reimbursement authorities in such a way that they are available for others to work with.

Current multi-use disease models are mainly exploited by companies or technology transfer offices (business and exploitation departments of universities and University Medical Centers). Licenses are often paid for by pharmaceutical companies (or other commercial parties) and free of charge for academic usage. For instance the UKPDS-OM uses a licensing system where commercial parties pay a fee for use of the model, whereas academic parties may use the model free of charge. For both types of use acknowledgements and proper reference is required by the University of Oxford. Other disease specific models owned by consultancy firms or academic parties have technology transfer officers who focus on licensing and have overview with regard to updates of the model.

A possible downside of licensing is that it may prevent some intended users from using the model because of the expenses. An upside of licensing is that the revenues generated may resolve issues surrounding funding for maintenance and hosting.

A.   Full HTA agency ownership
Full the HTA-agency ownership implies either direct public funding via the general the HTA-agency budget and/or licensing (i.e. asking a fee for model use) as an additional funding source. Given the complexity of the service provided a fee might not be out of place in this context. If a licensing system is employed by the HTA-agency it should be on a "not for profit, not for loss" basis.

B.   Private/Commercial ownership
The most straightforward method of raising funds for models by private and commercial parties is by issuing licenses. A possible downside of this system is that licenses could be very expensive, reducing use by smaller or less affluent organizations. In the case of mandatory use, high license fees would in the end imply higher product prices.

C.   Open source modelling (No single distinct owner)
In an open source scenario, no funding is provided by the users of the model, except sometimes on a voluntary basis. However, contributions to the product by the users can be considered as in kind funding. "General Public License" (GPL) exists to support distribution of open source software[40, 41]. This will also be useful for health economic decision models. The initial funding for development in many actual open source health economic decision models was a research grant. An important questions is: "Who will host (and maintain) the model, once the grant is expired, and what are the implications of hosting a model as far as ownership is concerned?" Options for funding are public funding for example by the HTA-agency or a different interested organization. A different option is by asking larger industry partners (pharmaceutical and/or medical device developers) to invest in maintenance and hosting, a strategy that is not likely to succeed since it is unlikely that industry partners are willing to invest in mechanisms possibly undermining their

market position. Small size, new developers aiming to enter the market may benefit from the investments made by the larger established parties. These larger parties are unlikely to invest in systems allowing easier access for new competitors.

D.   Academic cooperation scenario (HTA-agency+academic groups)
The main issue in this ownership scenario is the sourcing of funds. Clear and precise agreements should be made regarding what parties are responsible for funding development, maintenance and hosting and what will be given in return for the fee. Options for funding are public funding, licensing and research grants.

E.   Academic or other research institute ownership
Initial development by research grants brings the question how to maintain and host the model after the grant is expired. Licensing would be a logical solution. Payment could be dependent on user background, that is, a higher fee is asked from commercial users than from non-profit organizations. Examples are for instance the licensing of the EQ-5D questionnaires by the Euroqol Group and the UKPDS-OM diabetes model. Of note, some granting organizations require all materials (and models) developed during a funded project to be made publicly and freely available afterwards (open access). While in principle new versions would again be owned by the academic party, this suggests that open access would be a logical situation for models developed with funding from grants.

Topic 3: Liability and prevention of misuse
Liability is dependent on the choices made regarding ownership, mandatory use and prevention of misuse. The issue of misuse prevention is dependent on how the model is distributed, how distribution is supervised and how licensing is arranged. A free to use and unsupervised/unmonitored model is not subject to any prevention of misuse and therefore its outcomes may not be as valid as can be. Models that are mandatory to use for reimbursement decisions need more monitoring to prevent misuse since the decisions made based on the models may have far reaching consequences.

The owner of the model will likely be held responsible for preventing misuse by parties using the models. If the model is misused and a decision is made based on a misused model there is a chance that the owner is held responsible or liable for this decision. The only way for an owner to waive liability is by implementing clear terms and conditions for use and adaptation of a model. For instance, in the license for use of the UKPDS model it is literally stated:

"The University is a charitable foundation devoted to education and research, and in order to protect its assets for the benefit of those objects, the University must make it clear that no condition is made or to be implied, nor is any warranty given or to be implied, as to the accuracy of this Tool, or that it will be suitable for any particular purpose or for use under any specific conditions. Furthermore, the University disclaims all responsibility for the use which is made of the Tool. However, nothing in this statement will operate to exclude or restrict any liability which the University may have for death or personal injury

resulting from negligence. It is a further condition that the software obtained from this site is not distributed further without the same conditions and copyright statements being imposed. Those seeking to incorporate any part of the UKPDS Outcomes Model into other software projects must seek the permission of the copyright holders before distribution or publication of their software."

This outlines that clear and transparent terms and conditions may have a place in mitigating liability issues. Mandatory use may have an influence in the applicability of general terms and conditions because making use mandatory may result in a situation in which liability cannot be mitigated since decision making must be based on these models. Experts on liability mitigation with terms and conditions should be consulted to give a definitive ruling on this possible solution.

A.   Full HTA agency ownership
Misuse and liability has to be covered in detail and properly in licenses, especially when models are used on a mandatory base. The agency should stimulate and include supervision by the model-maintenance experts for the use and adaptation of the model. Using and adapting the model under supervision of modelling experts will reduce the possibility of misuse and thereby minimize the probability of making sub-optimal decisions. Responsibility to prevent misuse must therefore lie with the agency itself.

B.   Private/Commercial ownership
Liability should be properly arranged by the model owner. The HTA agency now is dependent on a "third" party for misuse prevention. Agencies taking decisions on these models should therefore adequately assess claims of liability mitigation by the owner of the model, and ensure that the model owner has adequate misuse monitoring in place. If a model owner claims to have adequate liability mitigation and misuse prevention measures in place, these measures should be assessed by HTA agencies to reduce the probability of making the wrong decision.

C.   Open source modelling (No single distinct owner)
For this business case, we do not expect substantial issues regarding liability for any outcomes resulting from using a model. There is however a liability for the reimbursement agency, as there is no or little oversight in use and modifications of the model. This could result in unreliable model results and the use of outdated models since there is no incentive to update the models.

D.   Academic cooperation scenario (HTA-agency + academic groups)
Academic groups will not be likely to accept liability as this not in their interest nor are they in the organizational or financial position to accept liability. As a consequence, liability should be covered by the decision making authority in this case. The model developer on the other hand is clearly identifiable and in this scenario, misuse prevention will mainly consist of good support to users.

E.   Academic or other research institute ownership
As academic groups will probably not accept liability this should be covered otherwise, for example by implementing strict terms and

conditions. Academic groups often require to be involved in applications as part of their access policy. This could assist in misuse prevention.

3.1.3 *Organization: topics not directly related to ownership*
Topic 4: Stakeholders role and collaboration.

Since they have a longer intended lifetime, requirements for multi-use disease models regarding acceptability to stakeholders and sufficient coverage of all stakeholders' insights is even more relevant than for single use disease models. Hence, as part of the development of the models different stakeholders need to be consulted. The stakeholders that need to be included are:

- Patients
- Care providers
- Health economics researchers
- Decision makers (HTA-agency/Healthcare Insurance/other)

For applications of the model again the appropriate stakeholders need to be consulted whenever the model is adapted to reflect specific situations. Ideally, collaboration with a panel of stakeholders is organized and continued throughout the entire period of model development, use, maintenance, and adaptation. Timely and proper inclusion of a broad range of stakeholders will enhance model validity as well as the acceptability of model based decisions to stakeholders.[42]

Topic 5: Software requirements

Software requirements depend on how access to models will be arranged: online through a user interface, or offline, that is, with the option to download the full model and run it on the user's own devices. A benefit of online models is the mitigation of liability, the prevention of misuse and it may resolve issues regarding licensing and ownership. A downside of online models is that model adaptability will most likely be limited.

If the choice is made to use offline models the software used for the models should be widely available and usable. Users and assessors should have easy access to the software in which the models are developed in order for them to be able to adapt the model to their specific situation. Transparency is quite important, to reduce issues regarding misuse. Issues will be mitigated because researchers will be able to examine and evaluate changes made by the users. See also section 3.1.6 on model transparency in general.

In a recent publication, TreeAge Pro, Microsoft Excel, R and MATLAB were compared across three qualitative criteria and two quantitative criteria, including transparency and validation, learning curve, capability and computational speed as well as cost of use.[13] The authors concluded that because of transparency advantages and efficiency in complex analyses MATLAB and R are favoured. Another publication compared Microsoft Excel with R and concluded that R and other modern programming languages allow for realistic modelling, quantifying decision uncertainty, are transparent and are reusable and adaptable.[43] Using a broader perspective than just HE decision modelling, many more software packages are available that are suitable

for simulation modelling purposes, and also general purpose programming languages are often applied.

Topic 6: Confidentiality
Transparency of the core model is key in order to promote the use among end users. An issue that may arise is that parameter values of innovations or pharmaceuticals inserted by developers is proprietary information and requires confidentiality. Models that have been adapted for a product and are submitted to reimbursement agencies should therefore be treated confidentially. For online use of models, the topic of confidentiality is more pressing, and puts requirements on the safety of the environment used to provide access to the model.

3.1.4   *Model development*
While in principle model development for a multi-use disease model would not differ from the approach for any health economic decision model, its suitability for various applications and interventions, and the wish to provide a model that is fit for use for several years, may stress the need for careful development with a keen eye on state of the art approaches. The panel and other advisors hence stressed the need to ensure careful development, mentioning a modular approach (Topic 7), balanced choices regarding model complexity (Topic 8), the potential of empty shell models (Topic 9), the need for transparency (discussed in section 3.1.7) and funding for development (discussed in section 3.1.2).

Topic 7: Modular approach
The scope of multi-use disease models will be typically larger than most single use models. Also, they should be suitable for the evaluation of several interventions, and should be able to account for interdependencies between consecutive treatments, when relevant. This implies that paying more explicit attention to model structure, for instance by using modular modelling, is probably more relevant for multi-use disease models.
The focus is on patient-level models, such as microsimulation state-transition models (STM)[44], discrete-event simulation (DES)[45], and agent-based models (ABM)[46]. These types of model allow to take patient characteristics and history into account, and will often be relevant when building a multi-use disease model, since they can flexibly handle interdependencies.

Definition of a modular approach
A modular approach to modelling means that a health economic model is divided in multiple connected modules, submodels, elements or components. These terms are used interchangeably below. Characteristics of a module are that (a) it has pre-defined functionalities, (b) it is a stand-alone (independent) element that is able to produce outputs based on provided inputs, and (c) it is re-usable. Modular modelling prescribes de disaggregation of the source code in multiple independent modules which are then connected, or communicate with each other instead of modelling all elements of the model in a non-compartmented source code ("single source code" from now on). For instance, disease progression and care pathways could be modelled as separate modules, which require a (partly) separate set of inputs[47]. Next to defining modules, models must also define how

modules interact with each other. For instance, the outputs of a "disease progression" module could serve as inputs for a "treatment" or "care pathway" module. Although methods for and examples of modular approaches to health economic modelling are (widely) available, these approaches are not (yet) standard practice among researchers, consultancy firms, and pharmaceutical companies.

The idea of modular modelling is not new in health economics; the ISPOR-SMDM Taskforce on modelling good practices wrote the following (2012): "To simplify debugging and updating, submodels should be used to structure the model. When comparing two or more strategies within the same system (e.g., for the same condition in a health technology assessment model), submodels common to all strategies (e.g., progression following disease recurrence) should be defined once and called from each strategy (i.e., all patients experiencing a recurrence pass through the common disease recurrence module)[48]."

Table 8 presents an non-exhaustive overview of existing modular models. They often focus on screening interventions and their downstream effects [51].

Table 8 Non-exhaustive list of example of modular models in health care

Authors	Model name	Model type	Disease area, context	Included modules
Habbema - et al - 1985[52]	MISCAN	Microsimulation	Cancer Screening	Disease and screening
Kolominsky-Rabas et al - 2015[53]	Prospective Health Technology Assessment (ProHTA)	Hybrid, combines system dynamics models for macro-simulation and agent-based models for micro-simulation	Mobile Stroke Units case study	Population dynamics.disease dynamics (e.g. incidence, prevalence, case fatality), health care financing, health care.
Trauer et al – 2017[50]	Australian Tuberculosis Modelling Network (AuTuMN)	Transmission dynamic model	Tuberculosis control interventions	Graphical user interface, input modules, data processing, model modules (model runner, disease-specific model, general transmission dynamic model), output modules
Treskova et al 2017[54]	None	Stochastic modular microsimulation	Lung cancer, screening	Population, natural history, clinical detection, survival, screening, and life history
van der Meijde et al – 2016[47]	Microsimulation for the Assessment of Individualized Cancer Care (MAICare)	Microsimulation Tumour growth module: Markov chains	Melanoma care (generalisable to other solid tumour types)	Disease model (tumour level and patient level), Clinical management module (diagnostics, treatment, surveillance)
Youn et al - 2019[51]	None	Discrete event simulations	Prevention of heart disease, Alzheimer's disease, and osteoporosis.	Heart disease model, Alzheimer disease model Osteoporosis model, Central routing point, end of simulation

The (dis)advantages of modular models
Modular modelling allows to disaggregate the complexity of the model, and to model each component of a decision problem more easily and accurately. Additionally, different modules may require different modelling paradigms, which is easier to accommodate with a modular approach. Another advantage of modular modelling is that not all stakeholders need to understand the entire decision problem but only require to be knowledgeable of "their" module[49]. Furthermore, dividing the source code in multiple smaller modules facilitates the detection of errors[50]. Modules can be independently tested, verified (code checking), and validated. Each module should be documented separately, which would increase the transparency of reporting and facilitate their adaptation and re-use. Besides, developing modular models forces developers to clearly define, not just the overall structure, but also the substructures (modules). When the same (single) adaptation would be required in a modular model or a model coded in a single source code, it is expected that modifying a module would be less challenging because the location of the adaptation would be more easily found and the change would only affect the outputs of the specific module. Expanding modular models may also turn out to be easier because model developers would "only" have to add an additional module to the already-existing model.

A disadvantage of modular modelling is that it may be more difficult to unravel how the full model works. The development of modules may clarify the overall structure of the model but structuring the model in multiple independent modules would require more time to develop than a single source code. Modular modelling therefore requires more careful coding than a model coded in a single source code. However, once a model has a certain degree of complexity, a clear structure of modules will pay off. A modular model might be slower than a model developed through a single source code, due to the required communication between modules. Finally, even though modules of a modular model may be easier to validate, it may be challenging to ensure that the combination of modules provide valid outputs.

Regarding model use, an advantage would be the re-use of modules which may avoid discussions about certain methodological choices of the assessment (assuming the modules have been developed according to the jurisdiction's guidelines). A modular approach may allow users to only run the specific module(s) they are interested in. Hence, the same modular multi-use disease model may be used for different types of applications, like cost-effectiveness assessments, budget impact analyses, or guideline development support. Additionally, modular models may enhance the communication of the model structure due to its clear compartmentation. Contrary to this, a modular structure may increase the technical complexity of the model, while the overall entire logic (and structure) of the complete model may be easier to understand by stakeholders.

Modules to be included in a health economic decision model
No methodological guidelines exist specifying which modules should be included in a modular multi-use disease model, due to little use of modular modelling in health economics. Table 9 provides a non-exhaustive list of potential modules which could be included in a modular multi-use disease model.

Challenges concerning the development of modular models in health economics

A first challenge is to decide which modules would be included and what are the boundaries of each module. Ensuring that elements are defined only once across all modules (single point of definition) and applying a consistent coding style across modules are additional challenges during the development of modular multi-use disease models[14, 50]. This is especially true when multiple model developers are involved, but once these challenges are overcome, consistent naming and coding style may improve collaboration between model developers and model code quality[50].

Table 9 Non-exhaustive list of potential modules

Type of module	Location in the model	Specific module topic/aim
"Care pathway" modules	Pre treatment	Population screening Diagnostic testing of patients
	During treatment	Treatment strategies Routine practice Monitoring Palliative care
	Post processing	Resource use and costs Quality of life/health benefits
"Disease and patient characteristics" modules	Modules for population at baseline	Patient characteristics Healthy population characteristics
	Modules to evaluate disease progression	Natural history of disease Population dynamics Survival
	Modules to summarize and aggregate outcomes	Discounting, calculate net present values, perform PSA and present its results
Analysis & Miscellaneous modules		Value of information analysis Multi-criteria decision analysis Graphical user interface

Criteria to determine when to develop a multi-use disease model using a modular approach are discussed in this paragraph. Highly complex models with an extensive 'breadth' may be the ones that benefit most of a modular approach because it allows to separate different independent elements in smaller chunks of code. When it is expected that the multi-use disease model will be used for a longer period of time, and may require several adaptations over the years, using a modular approach will turn out to be beneficial because adaptations are easier to execute in a module than in a large block of unstructured code.

Topic 8: Model complexity

For multi-use disease models to be useful, they should represent disease progression and treatment pathways with sufficient level of detail. One of the main challenges when developing a disease model is to find the right balance between the level of detail (model 'depth') and capturing all relevant aspects of multiple future decision problems (model

'breadth') [6]. These characteristics directly impact the complexity and usability of the model.

The ISPOR-SMDM Good Modelling Taskforce advises (2012) "Model simplicity is desirable for transparency, ease of validation, and description. However, the model should be sufficiently complex to answer the question at a level of detail appropriate for the problem being modelled and to preserve face validity to clinical experts. Greater complexity may be necessary in policy models that are intended to be used for many decision problems".[48] Additionally, Tappenden et al. mention that "[…] broader boundary of a whole disease model does not restrict the level of depth possible within the model"[6], meaning that developing a model capturing the entire disease pathway should not preclude a high level of details (within each module of the model). However both computation time and time needed for development and maintenance may become an issue.
Relevant questions within this context are thus (a) which element of the disease and treatment pathways should be included in a multi-use disease model, (b) what is a sufficient level of detail for a multi-use disease model, and (c) how should specific elements of the model that are not relevant for all assessments be handled.

A fundamental question when developing a multi-use disease model is determining the boundaries of the model (model 'breadth')[6]. This question is closely related to the health policy decisions that the multi-use disease model is intended to inform. The more diverse the policy decisions that should be informed by the model, the more extensive and complex the model [48]. Indeed, models capturing the entire disease trajectory from screening to palliative care may be highly complex. This complexity may in turn hamper model understanding by stakeholders, and may undermine trust in model results. This can ultimately hinder the use of the model. Furthermore, very complex models also bring high development and maintenance costs. However, from the perspective of other simulation modelling fields, health economic decision models are not particularly complex, even those with a wide scope.
Using a modular approach may partly address this, see also Topic 7 above.

Complexity could lead to issues relating to computational power and/or time to run analyses[51], which may hamper the practical use of the model to inform health policy decisions. One could therefore decide on developing less complex modules (or models) which are easily adaptable and transferable. These issues are also discussed in 3.1.7.

Concerning the last issue (c), model developers could ensure that specific computations could be disabled when these would be considered irrelevant for a specific health policy decision. This poses several additional challenges and involves implicit assumptions concerning the disabled computations. [55] An alternative to this approach would be to allow users to explicitly replace highly specific computations by approximations[56]. Both require validation. Alternatively, modules could be made available for re-use to offer various more or less extensive model variants.

Summarizing, decisions concerning model depth and breadth are hard to take and do require some overview of envisioned model applications. The wider the range of applications, the more depth and breadth is required, however, this comes at a price of increased model complexity and input data requirements. For multi-use disease models, the balance is more towards additional detail than for single use models. Modular modelling can then be instrumental in keeping the overview and allowing for selective maintenance.

Topic 9: The role of empty shell models
In the literature, a number of model structures have been published.[14-18] These offer what we may call "empty shell" solutions for health economic models. They offer a well-developed computer code for a typical health economic decision model, however without input data or estimates of model parameters. This is left to the model user. In terms of modular modelling, several modules are provided, but not the input data. Sometimes modules for input parameter estimation are also provided, but not the data themselves [14-18].

This brings some advantages, for instance offering users well tested and hence presumably error free code. A drawback is a lack of flexibility to adjust a model structure to a specific disorder. A more important drawback is that these models leave the estimation of model parameters and input data to each specific user, while this is quite important in terms of consistency. So while empty shell models do help improve consistency and improve efficiency as well as transparency in coding, they do not solve parameter or structural uncertainty and do not serve as a workable solution on their own. Empty shell models however could serve as a basis for a multi-use disease model.

3.1.5   *Input data*
Any health economic decision model uses input data and these play a crucial role in the assessment of model validity as well as in the judgement concerning model outcomes. Regarding the application of multi-use models, some specific challenges arise related to the input data used to populate the model.
Some panel members suggested that patient level models, based on patient level data, might encounter issues regarding the privacy of the individuals whose data are applied and that multi-use might aggravate this issue. The team discussed this and considered the possible situations in which this would become an issue. In Topic 11 we describe more elaborately what GPRD compatibility issues may arise and how the organization around model access, model storage and model results access and storage should and could deal with this. A related and possibly more relevant issue is the concern expressed by some panel members that (trial-) data needed to populate models are proprietary (Topic 10)

Topic 10: Access to patient level data, especially on effectiveness.
Trial data on effectiveness of new treatments may be applied in a single use model, where the owner of the data has a clear interest in making them available. For instance, when a pharmaceutical company has financed a trial for a certain new medication and is also financing the

health economic decision model to evaluate this medication for cost-effectiveness. This is a very common situation. The access to this type of data for a multi-use model might be problematic.

Two possible solutions exist. First, when multi-use models would become the standard, owners of multi-use models could force access to trial data. Such access is considered acceptable for drug approval processes performed by EMA and FDA. When the owner of the multi-use model is to be a similar regulatory authority, this may be an option. So for scenario's A and D in our list of possible ownership scenarios this might be a future option.

Alternatively, developers and owners of multi-use models can rely on alternative sources of data. These are published effectiveness studies and observational data. Given that care as usual is often chosen as the comparator intervention, for this comparator intervention patient level data could be obtained: from registries, administrative data sources, and cohort studies. Very often indeed this type of secondary, observational data have been applied as input data for multi-use disease models, in combination with published information from effectiveness trials.

Many observational data are accessible open source at an aggregated level (for instance VEKTIS open data, GIP, statistics Netherlands), while other data owners publish key characteristics of their cohorts. When for the estimation of specific model parameters access to the original individual level data is needed, this may requires contracts with institutions such as Statistics Netherlands and Vektis, or with research groups having performed cohort studies. Such contracts often require stating a very specific purpose of the data analysis, and when a research group is involved, often include the co-authorship on resulting publications. Use of data to estimate a parameter in a health economic decision model that is intended for repeated use and requires some maintenance is a-typical for data owners. Some creativity is required for suitable contracts, especially when the models will be applied and possibly adapted by external parties.

Topic 11: Compatibility with GPRD

In principle, when patients provide informed consent for the use of their data in a health economic decision model, this would cover its use for a specific purpose, for instance the evaluation of a specific medication. When instead a multi-use model is going to be developed, of course consents should be adapted to this. However, it is quite rare that patient level data are gathered for the sole purpose of health economic model development. In general, data used for a health economic decision model are taken from existing datasets, to which access is granted for the purpose of model development. In that case, no difference will exist between arrangements needed for a single use or a multi-use disease model.

Furthermore, most current patient level models are not patient level in the sense that they model heterogeneity very elaborately and at the individual level. Rather they are structured in this way to handle complexities more easily, and to cover the effect of a limited number of co-variates. This implies that for most patient level models, as well as for all cohort level models, patient level data will be used to estimate model parameters that cannot be traced back to individual patients and imply little to no privacy issues, once they have been estimated.

Organizations storing microdata will have procedures to ensure sufficiently anonymous data are extracted from their data.

3.1.6   *Validation and Transparency*
Challenges related to uncertainty, validation and transparency that were mentioned by the experts in the panel survey consisted of the communication of model limitations, transparency of model structure, assumptions and input data, the risk of a single multi-use model being a blinder for structural uncertainty, and the comparability with other models/model outcomes. These are discussed together, because addressing each of these challenges contributes to the salience and credibility of a decision-analytic model.

Topic 12: Uncertainty analysis, Model validation and Transparency

Most of the challenges related to these topics are not specific to multi-use disease models. Existing guidelines and tools such as the ISPOR-SMDM modelling good research practices,[48] the Philips checklist[57] to assess decision-analytic model quality, the TRansparent Uncertainty ASsessmenT (TRUST) Tool to identify and assess uncertainties,[58], the Assessment of the Validation Status of Health-Economic decision models (AdViSHE)[42] tool to assess model validation status and the TECHnical VERification (TECH-VER)[59] tools for code verification could all be used. Use of these tools will help to communicate model limitations, to identify and assess uncertainty as well as to perform and report on validation efforts. Identification of uncertainty through the TRUST tool includes structural uncertainties that can subsequently be explored through scenario analyses, parameterization of the identified uncertainties and/ or model averaging.[60, 61] Validation should cover conceptual model, input data, code or software, and model results. One of the validation tests (next to face validity tests, comparison to external data, and comparison to internal data) is cross-validation. This can be done by comparing to other disease models or with previous model versions after updating. Several panel members expressed the need to keep open opportunities for these types of validation tests. Multi-use disease models do not rule out the existence of competing models, and cross validation activities in practice have additional value for both model users and model developers when disease simulation models are repeatedly applied and maintained over a longer period.[29, 62] The use of a modular approach (see page 18) to develop the multi-use disease model might facilitate these comparisons as different parts of the model can be (cross-)validated separately.

Next to uncertainty and validation (how well the model reproduces reality), model transparency (how easily people can understand the model's structure and application) is an essential aspect to increase trust in/credibility of a multi-use disease model.[63] The development of multi-use disease models could be considered as a step towards transparency because, by nature, these models separate the model building activity from specific applications. This provides an opportunity for transparent reporting of model structure and validation steps, independent of the nuances of individual policy questions. Similarly, individual applications of multi-use disease models will have more opportunity to elaborate on the adjustments made for the particular policy question.[64]. Model transparency is generally focused on

carefully describing what the model does and how. This would allow reviewing the model's structure, equations, parameter values and assumptions and hereby helps to understand the model limitation as well as potential applications.[63] Transparency might be achieved through 1) the production of non-technical documentation for the interested reader to understand and interpret the model results and 2) technical documentation written in sufficient detail to be able to review and/ or replicate the model for the reader with sufficient expertise, 3) open source data and version control. See the ISPOR-SMDM paper on model transparency for suggested minimal reporting for the (non-)technical documentations.[63] The non-technical documentation could be publicly available (or to all who ask for it) while the availability of the technical documentation might depend on the business model and could be made available openly or under agreements that protect intellectual property and/or commercial interests. These agreements could potentially focus on allowing access to a model with the aim to assess its credibility rather than modifying the model for other purposes than the developers originally intended.[11] Next to protecting intellectual property (including academic awards) and/or commercial interests, other main barriers to making the technical documentation publicly available are potential loss of control, potentially leading to misuse of the multi-use disease model and additional efforts demanded [65] (more barriers being mentioned in the literature, see for instance.[64]). However, several examples also exist of very elaborately documented models.[66, 67] In practice rebuilding a model for the purpose of replicating, even when all equations are made publicly available is a resource intensive and little rewarding task, which might be illustrated by the limited amount of published model replication studies.[68] Hence, providing a detailed technical documentation with equations, but without providing an executable version of the model, might seem as an ideal balance between being transparent and protecting intellectual property, commercial interests and/or against misuse. However, it can be very challenging to understand how a model works by only examining its equations. Even if this seems to be valid, it is virtually impossible for anyone to determine a model's accuracy by "running" it in one's head. Even a detailed technical documentation with equations hence does not provide full transparency unless the reader has the resources to actually implement it [11, 63]. Therefore, it might be preferable to provide access to an executable version of the model. Alternatively, if a detailed technical documentation or executable version of the model is not available, there might be an increased emphasis on validation tests to increase trust in / credibility of the multi-use disease model. See for example available Diabetes models, where users are only given partial access to the model (i.e. only a user interface) while model trust was built by demonstrating model validation.[25, 29]

3.1.7 *Model use*
Topic 13: Transferability.
Description: challenges related to transferability are not specific to multi-use disease models, although these can be more prominent and/ or slightly different when compared to traditional single-use models. It is generally believed that the degree of generalizability differs for the different input parameters in a health economic model (See Figure 7). For instance, cost prices and discount rates are likely to be context

specific and do have a high need for (transferability) adjustments while the relative clinical effectiveness of a technology is more likely to be generalizable and hence has a lower need for (transferability) adjustments. Multiple checklists exist to examine the need for transferability adjustments for cost-effectiveness studies. These checklists have only limited attention for aspects of the health economic decision model. (Table 10)

Moreover, most of the literature related to model transferability focuses on transferability between different countries while transferability adjustments for multi-use disease models developed for the Dutch setting (particularly from the National Health Care Institute perspective) are probably more focused on transferability for specific applications/decision problems. This also closely relates to bias and indirectness as a source of uncertainty as defined in the TRUST tool[58] (discussed in previous section). Hence, the TRUST tool can potentially be used to identify potential transferability adjustments for specific applications/ decision problems.

Different types of input parameters, that might require (transferability) adjustments, should be easily adjustable in multi-use disease models. This can potentially be done through a modular approach, using different modules for different input parameters such as unit prices and resource use allowing to incorporate setting specific costs. (see section on modular modelling above)

Figure 3 Balance between the need for transferability adjustment and the degree of generalisability. Source: Knies [58]

Table 10: Items in transferability checklists that relate to HE decision models

Author	Items related to HE decision models
Heyland et al [69]	• From clinical generalizability: Are the patients described in the analysis similar to those patients you see in your own setting?
Späth [70]	• Characteristics of the treated patient population
Welte et al [71]	• The case-mix of the target population, such as age, sex, race, education, co-morbidity, severity of disease and risk factors • Disease prevalence/incidence • Life expectancy
Boulenger et al [72]	• Is the target population of the health technology clearly stated by the authors or when it is not can it be inferred by reading the article? • Are the population characteristics described? (e.g., age, sex, health status, socio-economic status, inclusion/exclusion criteria) • If a model is used, is it described in detail? • Are the origins of the parameters used in the model given?
Drummond et al [73]	• The case-mix of the target population, such as age, sex, race, education, co-morbidity, severity of disease and risk factors • Disease prevalence/incidence • Life expectancy
Turner et al [74]	• Safety domain: • Does the population described for eligibility match the population to which it is targeted in the target setting? • Are there any reasons to expect differences in complication rates (e.g., epidemiology, genetic issues, health care system)? • Effectiveness (including efficacy) domain: • Would you expect the baseline risk of patients within your own setting to be the same as the baseline risk of those patients considered within the HTA report for adaptation? (assuming that patients receive the same treatment and same comparator)
Antonanzas et al [75]	• Critical objective factors: • The relevant parameters needed to calculate the ratio cost/effectiveness are given in the study. • Noncritical subjective factors: • The model connecting variables and parameters can be adapted to the new context. • Life expectancy is similar in both contexts.

Topic 14: Access for users (practical)

The required (level of) access to multi-use disease models will depend on the (obligatory) use, development, maintenance and funding of the model. If it is obligatory to use a multi-use disease model for certain disease areas (e.g. for developing a pharmacoeconomic dossier), the level of access (as well as technical documentation and an accessible interface) should be guaranteed to satisfy these requirements (e.g. future access could be ensured by having a minimal level of model maintenance, so that the code still runs on modern computers). Therefore, the required access should be provided with appropriate licensing that might involve financial contribution to the model development and maintenance but also consider topics such as misuse

and liability for the model results (see also sections above). This should be weighed against freedom of users to adjust the model to their own requirements and/or data.

Several panel members suggested to apply the principles of FAIR data. This would imply FAIR multi-use disease models:

- Findable (for instance in a model registry, like the Diabetes simulation modelling database[76] and the CISNET model registry[77],
- Accessible (this can take various forms, from fully open source code running on free software to information about a contact person),
- Interoperable (which in case of multi-use disease models refers to their transferability and flexibility),
- Reusable (which in case of multi-use disease models refers to transparency, model maintenance and user support).

Topic 15: Limits to acceptable run time/software

The run times of a multi-use disease model depends on the software used as well as its implementation and can be a barrier for its use as well as its validation. The maximal acceptable run time will depend on the relevant process timelines for the (obligatory) use of model. It should be feasible to use and validate the model within the given timeframe, especially if its use is obligatory. Again, this is not specific to multi-use disease models, but can be more prominent for complex models (which is likely applicable to the majority of multi-use disease models).

3.1.8   *Model results*

Topic 16: Governance for access to model results.

Depending on how much of the model is open source, it is important to specify how to handle the output data. Two important aspects are the interpretation of output data and the access to output data.

Proper interpretation of output data requires extensive documentation and a manual of the model. This should specify what the model's scope is and more importantly, what is outside of the model's scope and for what analyses it can and cannot be applied. For instance, the model could be very well suited to calculate outcomes for the overall Dutch adult population, but be ill-equipped to calculate valid results for very specific subgroups.

The second aspect concerns the possible request for confidentiality of the model outcomes, for instance if the model is applied by a pharmaceutical company in the market access process of a new drug. In these cases, the company may be worried about confidentiality when it for instance has to access the model through an online tool and provide its (confidential) parameter estimates in this tool. Of course, this issue would not exist when the company could download the model and run it on its own devices. This however sometimes brings questions regarding the fidelity of the model software. Solutions for the first issue would be proper documentation and clear guidelines regarding model use. Solutions for the second issue are very much linked to model governance. Software solutions exist to govern this properly.

Topic 17: Improve model understanding (explanation).
This concerns the need to ensure that model users do sufficiently understand the outcomes of their analyses. This may be hard since they did not develop the model themselves. It is very similar to the issue of proper application and interpretation of model results, as well as the issue of transparency and hence the approaches to solve this issue are described above.

3.1.9   *Model maintenance*
This category of issues is closely linked to choices made regarding ownership.

Topic 18: Need for official updates
When a multi-use model exists over a longer period and several parties apply it for their own purposes, the risk exists of an uncontrolled growth of different versions of the model. This complicates model validation, for instance using specific population data. It also complicates the comparison of (health economic) outcomes resulting from application of the model. Hence -depending on the choice of owner- the owner will need to control the availability and use of different model versions to some degree by issuing official updates. This requires proper maintenance of the model and hence, funding and expertise to do so. Scenarios A (Full HTA agency ownership), B (Private/Commercial ownership), D (Academic cooperation scenario), and E (Academic or other research institute ownership) would all have a specific owner who would be qualified to perform version control. The open source scenario does not have a specific owner and in that situation official releases would be less obvious. It is then up to the community of users to ensure that existing model variants are validated, and – if not valid enough- also discarded in a clear way. Version control as described in 3.1.9 below is a relevant solution strategy that can be used by the model owner as well as the modelling community.

Topic 19: Sustainable knowledge base
This issue links closely to model transparency and documentation. Often personal communication with a known model expert that guides the new model user through an existing model is more helpful than elaborate published documentation. Hence models depend often to a large degree on experienced model users. This is what is meant by a "sustainable knowledge base". When only a single individual is the entire knowledge base that is not a very sustainable situation.
Scenario A bears some risk here, when the model development does not take place at the same institute as the model ownership. The same may hold to a lesser degree for scenario D. Scenario B, with commercial ownership is at risk when the commercial party is relatively small. This also holds for academic ownership, with a large reliance on -notoriously unreliable- funding in an academic setting. Scenario D may avoid some of the disadvantages of A and E, by offering more stable funding, in combination with development by the owners. Scenario C (Open source modelling) brings its own solution: once a blooming community exists, the knowledge base is sustainable, but if that does not happen, it is difficult to enforce it.

Topic 20: Adaptability of model and approval of adaptations
New model adaptations could in theory be developed by a wide range of model users, both academic groups as well as commercial parties, with possibly a conflict of interest. The model owner has to find a procedure to approve adaptations and to check them for content. Also model users should be sure that they can rely on the model version which they use (see also need for official updates above). When allowing external parties to adapt the model, this may result in the owner/developer spending a large amount of time in defending and explaining all the many model assumptions .

An (idealistic) possible option would be to have an open source model and allow the community of researchers to improve and extend the model. This is the shareware solution, and links to scenario C. This ensures maximal adaptability, but comes at a price.[43] Governance is required in order to keep track of model versions and distinct validated from non-validated versions of the model. In software development, elaborate experience exists with this process. Version control software, such as subversion or GIT, can be used to keep track of modification to the source code.[78] Version control software allows for governance of versions by comparing earlier versions of the model to adaptations of the model. In case of an adaptation, which for instance contains a mistake or is not (yet) validated, an earlier version of the model can be evoked, with minimal disruption to the users. Version control systems can thereby also restrict adaptations of the model to specific parts of the model, but keep the core of the model unadjusted. Governing the model should include thinking about which parts of the model, and also for instance the interface, may be adapted. Furthermore, there should be a governing party assigned, even in case of option C. (Open source modelling), which allows (or rejects) the model adaptations into an official updated model version.

User interfaces can allow a wide range of model settings to be adjusted relatively simply by model-users. These include population characteristics, intervention scenarios, time horizon, number of runs, discount rates, perspective, and sometimes even unit prices and several choices for structural model parameters. Examples of user interfaces in open source models highlight this.[79, 80]
Any updates that cannot be implemented via the user interface requires adaptation of the underlying model code. Such adaptations typically imply the need for validation and elaborate testing, before the new model update is formally released.
Updates of model input data, that would translate to new model parameter estimates are usually also not easily implemented via an interface, since the pre-processing of input data to estimate model parameters is usually not included in the model itself. While most parameters relevant for the health economic evaluation would normally be included in the interface, users would be responsible for proper pre-processing and such updates would normally also require new validation and testing efforts and official releases.

3.2 Blueprint for organizational and methodological issues in relation to ownership choices

The structure of this blueprint is organized based on the 5 different business cases based on ownership choice that we distinguished above. These are repeated here for clarity.
   A. Full HTA agency ownership
   B. Private/Commercial ownership
   C. Open source modelling (No single distinct owner)
   D. Academic cooperation scenario (HTA agency+ research group)[2]
   E. Academic or other research institution is owner

These ownership choices impact certain organizational choices (mandatory use, maintenance and hosting, liability and prevention of misuse) as well as financial consequences. The resulting business cases are described below. Three remaining aspects of organization do not directly relate to the choice of the business case. They concern stakeholder involvement, IT infrastructure and software, and security of model information. The discussion regarding the financial consequences has its focus on the implications for the HTA agency. Of course, the other stakeholders will also experience different financial consequences of the different business cases.

3.2.1 *Discussion of organizational choices for 5 business cases*

In theory, it is not obligatory to have a once and for all decision for one of these business cases. A pragmatic choice might be to use the available multi-use disease models and take for granted the ownership structures offered, resulting in a mix of business cases. However, some business cases, especially A, but also D, do require substantial investments in in-house expertise and infrastructure from the HTA agency. For instance, hiring people with modelling expertise to support business case A (or D) will only be efficient when more than one model is to be supported. The same holds for contracting with third parties, using the same organizational structure for all multi-use disease models will be more efficient and allow to work with more standardized contracts and tendering procedures.

A. Full HTA agency ownership

While models might be developed by other parties, this business case assumes the model is fully owned and maintained by the HTA agency, who also supports its use. Mandatory use in reimbursement dossiers, or as part of guideline development is possible, since the HTA agency could require this as part of its procedures. Maintenance, helpdesk and hosting have to be financed by the HTA agency who might use license fees to raise funding for this. Mandatory use in combination with license fees might be problematic when fees are perceived to be higher than costs. With a single owner, liability is clear, and will have to be regulated, especially in case of mandatory use. Regarding misuse, an advantage is that the HTA agency has full overview of model use and adaptations of the model and is free to organize model access to avoid misuse. It seems most logic within this business case, that all multi-use

[2] Next to academic groups, other research institutes develop HE decision models. In the text below, when academic group is mentioned, this should be read broader as any not for-profit research institution

disease models in a certain jurisdiction have the same owner, the HTA agency in question.

Existing practice shows partial examples of this business case, in that for instance the Belgian Healthcare Knowledge Centre (KCE, kce.fgov.be/) develops its own models or commissions models via tenders. However, as far as we know, these models have only been applied by KCE researchers and are not made available to third party users.

This business case requires a relatively large initial investment by the HTA agency, to hire sufficient expertise, both (scarce) modelling and software engineering expertise as well as legal expertise. For each multi-use disease model, the initial development has to be financed and organized in-house, or bought externally. Maintenance, access, and support has to be organized in-house, requiring an adequate infrastructure and hence requiring money and staff.

B. Commercial ownership

Mandatory use in case of commercial ownership is problematic, since model users are required to apply (and pay for) a model owned by another private and for profit party. This commercial party, as the owner of the model, is liable for the contents of the model, has to ensure sufficient maintenance and enable access to model users. Usually, a license fee will be raised and this will be a commercial tariff. The HTA agency has a choice to either contract commercial parties to develop certain models, with the option to cover in these contracts the height of license fees, minimum maintenance and requirements for hosting. Alternatively, the role of the HTA agency is more limited and consists of expressing a preference for certain existing commercial models (a system of recognition by HTA agencies of existing models). Misuse prevention, like maintenance, is the responsibility of the model owner, and the HTA agency has limited ways to influence this.

Existing practice shows several commercial multi-use disease models exist, and few have also been recognized by HTA agencies.

When this business case works with a system of preference or recognition, initial investments that the HTA agency has to make are limited to the resources needed to produce an inventory of suitable models. In-house expertise to judge model validity and model suitability for purpose will be needed. When no suitable model can be identified, for some disease areas, the HTA agency has to order the development of a new model, which is associated with additional expenses. Notably, costs for model-users could be high when commercial parties ask high fees for model use.

C. Open source models

This scenario implies that multi-use disease models are made available as open source models, without a specific owner. However, a governing organization still needs to be assigned to allow the adaptations of the model into an official new model version. Mandatory use could be an option, since models would be available at no costs. General Public Licences have been developed to cover liability and allow access. Only voluntary contributions to maintenance and hosting costs could be raised, which implies that organization of maintenance is an issue and requires a dedicated party with sufficient own resources. Some existing platforms might however be used for hosting.[81, 82] Prevention of

misuse is hard because there would be no identifiable owner being directly responsible or having an overview of existing model adaptations.

Several existing multi-use disease models have been made available as open source.[11, 12, 26, 83] Some require registration of users, which brings a certain level of control.

When this business case works with a system of preference or recognition, initial investments that the HTA agency has to make are limited to the resources needed to produce an inventory of suitable models. A considerable amount of in-house expertise will be required to judge model suitability and model validity and possibly also to support model users. When no suitable model can be identified, for some disorders, new models may have to be developed. In that case the HTA agency has to order the development of a new model, which brings costs, and require that the new model will be made available as an open source model. The model developers need to have incentives to produce an open source code. Notably, costs for model-users would be low. Further development might be provided in-kind by these model-users.

D. Cooperative ownership
This business case builds on joined ownership by an HTA agency and a non-for profit research group, who has developed/has to develop the model. The research group could vary per model, with the HTA agency having the overview over the set of multi-use disease models available. Mandatory use is possible, as the HTA agency is in control of the set of available models. Liability and licensing now requires careful contracting, to clarify the role of the respective joint owners. License fees could be applied to finance maintenance and hosting. These tasks could be delegated to model developers, who would hold the expertise to support model users. Misuse prevention would be a joint task. In practice, model developers could offer support to model users to prevent misuse. Many research groups for instance require an upfront project proposal and to be included in any model application, in order to keep some control over applications.

While examples exist of models owned by non-for profit research groups, we are not aware of examples of joint ownership.

This business case would require initial investments, both to support a certain amount of in-house expertise and to support building an infrastructure to organize access and liability. Also a procedure is needed to select existing models or commission new models. Support and maintenance could be organized by the research group, hence would not require financial resources and/or capacity from the HTA agency. Some degree of flexibility exists regarding the division of responsibilities between both model-owners. The HTA agency has some control on the costs charged to model-users.

E. Full ownership by non-for-profit research group
For ease of reference we call this academic ownership, but any research institution would qualify here. This business case assumes the HTA agency refers model users to models that are owned and maintained by not-for-profit research groups. These groups can organize licensing and access, and are responsible for maintenance, support and distribution, as well as misuse prevention. Different modelling groups could develop different models. In theory, several multi-use models for a certain

disease could be recognized. Like with commercial ownership, mandatory use is somewhat problematic, since a third party is involved. Liability should be covered by the model owner, examples of licenses used by research groups exist. Most model owners require project plans and being involved in model applications, allowing them some control over misuse.

Several examples from practice exist, for instance the UKPDS-OM Diabetes model[26], and also lessons can be learned from the way access to questionnaires like the EQ5D health status questionnaire is being organized.[84] For other models, access has been organized via a contact person, for instance in the model registry of CISNET.[77]

Like cases B and C, this business case could work with a system of preference or recognition, requiring limited initial investments to produce an inventory of suitable and valid models. In-house expertise to judge model suitability for purpose will be needed. When no suitable model can be identified, for some disorders, new models may have to be ordered by the HTA agency, which brings costs. Costs for model-users depend on the level of license fees required for model use. Not-for-profit model owners should not ask for fees that exceed their costs, and often ask somewhat higher fees for commercial use, to allow low or zero fees for non-commercial applications.

3.2.2   *Methodological issues and their link to the 5 business cases*
Choices regarding ownership also affect possible and desirable solutions for several methodological issues. For other issues, potential solutions have little link to the chosen business case. However, the financial consequences of the selected business case usually will affect how multiple methodological issues are solved. Figure 8 illustrates this.
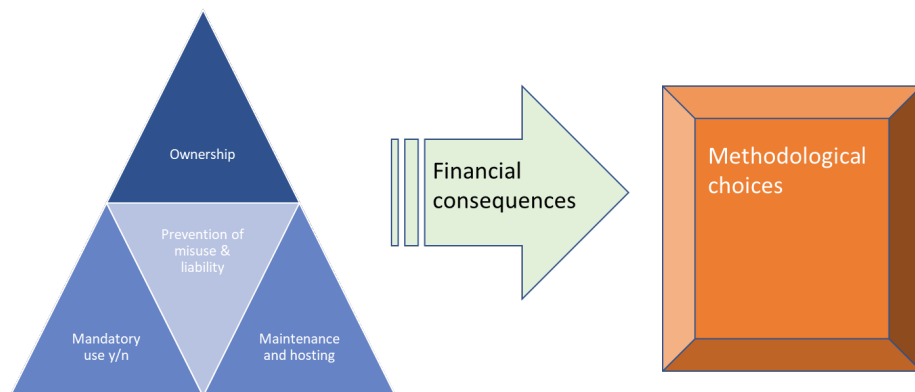

Figure 4 The interrelationship between organizational choices, financial consequences and methodological approach

Methodological issues that are independent of business scenario
Modular modelling, model complexity and model run-time, as well as choices regarding software are issues that require attention during the development of any health economic decision model. For multi-use disease models, these issues might arise somewhat more prominently. Since multi-use disease models are usually more complex than single use disease models, and since they are intended for multiple use, model flexibility (for adjustments) and ease of maintenance are more important than for single-use models.

Choices made concerning these model development issues will affect the suitability of the model for various applications and the accessibility of the model for model-users, both regarding technical ease of access and in terms of understanding what the model code is doing and why.

Methodological issues that do vary with business cases
For these issues, the chosen business case will affect the possible options.

Transparency and validation
Sufficient transparency and a good validation status are paramount to ensure the credibility of a multi-use disease model and trust in model outcomes. Of note, validation status may vary with the application at hand, that is, a model that is valid enough for a specific application, may need to be validated again for different applications.

- For the business case of a HTA agency as single model owner (A), the agency has freedom of choice regarding the mix of transparent model documentation, code accessibility, and validation testing. The full responsibility to organize this is also with the HTA agency.
- For the business case of commercial ownership (B), usually model programming code is not fully accessible. Clear documentation and elaborate validation testing in contrast tend to be available, since the model owner has an incentive to support the reputation of their model and enhance its credibility.
- For open source models (C), the programming code is by definition fully accessible. While in theory completely transparent, this would not suffice for complex models. Additionally, lack of documentation and validation status may hinder the model's credibility.
- For cooperative ownership (D), full access to code for the HTA agency, as an owner of the model could be agreed upon in the contract. However, for external model users, probably partial access combined with clear documentation and validation tests like in case B will be desirable. The amount of documentation and validation testing will partly depend on available resources for model development and maintenance.
- For ownership by a not for-profit research group (E), like in B and D, a mix of partial access, documentation and validation testing is the most probable choice. Full code access may cause problems regarding intellectual property, and if licenses are issued at a cost, full code access is seldom seen. Involvement of experts from the research group that developed the model will often support access further.

Transferability
Multi-use disease models have to be applicable to the jurisdiction of interest for the HTA agency, in this case the HTA-agency.

- For the business case of a HTA agency as single model owner (A), the agency could ensure the model is applicable to the setting of interest. Developing models for the purpose ensures this, but brings high costs. Transferring an existing international model maybe a more feasible option.
- For the business case of commercial ownership (B), existing models are mostly international. Adaptation to the local setting

(transferring the model) will come at a cost. Commercial parties in general have experience with this approach.
- For open source models (C), transferability is to some extend expected, but is not guaranteed. Adaptation to local circumstances has to be performed by the model user.
- For cooperative ownership (D), the most likely situation is that the new or existing model has been developed for the local setting.
- For ownership by a not for-profit research group (E), new models will also most likely be based on local data and fine-tuned to the local setting. However, research groups may also have existing models that could be transferred to the local setting. In this case, transfer is the responsibility of the research group(s) involved and options depend on data-availability and -access.

Access and support for model users
This mostly concerns the structure of the model and its software, as well as the IT infrastructure on site of the model owner.
- For the business case of a HTA agency as single model owner (A), the agency could ensure easy and safe access with sufficient support, both IT support and support regarding model content.
- Commercial owners (B) have experience in organizing this. Often support is offered against paying a fee, while access is through an interface.
- For open source models (C), platforms exist to support access to model code. Little to no support is usually available to get the model up and running or for questions regarding model interpretation. An active online community of users could substitute official support, but opinions differ on how well this ensures quality. In practice, a core team with the resources to keep the overview and offer basic support is usually present.[85] As a recent example the Dutch development team of the corona app is using a combination of a certain degree of control by a core team with open source, soliciting comments from a larger community.[86]
- For cooperative ownership (D), the HTA agency and the research group could decide who will host the model and who will organize the support. The research group, provided they have sufficient capacity, usually is able to offer the support.
- In case of full ownership by a not for-profit research group (E), this group has to make sure their institute offers both infrastructure and capacity for access and support.

Privacy and data safety issues
This closely relates to the organization of access above, but also concerns storage of model outcomes. Online access would require extra attention.
- For the business case of a HTA agency as single model owner (A), the agency should ensure safe storage of data. The reputation of the HTA agency may be helpful here. Currently, as part of reimbursement dossiers, parties are used to share data and model code with the HTA agency.
- Commercial owners (B) have experience in organizing this.

- For open source models (C), the issue will not so much be the safety of model outcomes, since usually access to the model code is provided and models can be run locally and offline. However, safety of the model code could be an issue, platforms have to be trustworthy.
- For cooperative ownership (D), the HTA agency and the research group would organize this together. Involvement of the HTA agency could help as a guarantor since experience exists in sharing information between companies and HTA agencies.
- For not for-profit research groups (E) as model owners, examples exist of how this has been organized. The main problem with this business case might be the safety/confidentiality of model outcomes, which has to be guaranteed to model users, especially in case of online access.

Validity of updates
Ideally the HTA agency issues a final judgement on all updates/model adaptations. Regular maintenance of the model is needed, at the very least to keep the model up and running on modern computers and to fix essential bugs. Depending on the intended applications, model parameters will also require regular updates.
- For the business case of a HTA agency as single model owner (A), the agency would need to organize this, and hence have capacity and expertise on model validation and regarding the contents of the multi-use model, as well as access to input data for parameter updates.
- For a commercial ownership situation (B), the HTA agency would have less control on model validation tests, and model maintenance. A commercial party may decide to stop maintaining a certain model, although contracts could be used to ensure maintenance is continued.
- For open source models (C), validation and maintenance is not guaranteed.
- For cooperative ownership (D), validation and maintenance are expected to be part of the agreements. When third parties own registries needed for maintenance of crucial model parameters access needs to be organized.
- For a not for-profit research group (E) as model owners, the situation is comparable to B.

Model flexibility
This concerns the degree to which the model can be adapted to new applications.
- For the business case of a HTA agency as single model owner (A), the HTA agency would need to ensure sufficient flexibility in the model design to accommodate easy adaption to new applications.
- For a commercial ownership situation (B), access to the full model code is not provided, but the model can be accessed via an interface. In that case, model users have less flexibility to adapt the model to their specific application.
- For open source models (C), model flexibility will vary. For newly designed models that were intended to be multi-use disease models, flexibility might be sufficient.

- For cooperative ownership (D), for newly developed models, this can be taken into account. However, when access is organized via an interface, less flexibility will be present to model users. Also for existing models, flexibility could be less than desirable. Extended flexibility may, however, be requested and will also develop over time
- For a not for-profit research group (E) as model owner, flexibility offered will be influenced by the group's capacity and resources, and its eagerness to promote the use of their model.

3.3 Overall summary Blueprint work

3.3.1 *The potential benefits of introducing multi-use models*
The discussion of topics in section 3.1, along with the business cases for implementation may have left the reader with the impression that multi-use disease models bring a lot of challenges. However, a very important advantage is the reduction of the inefficiency involved in repeated development, and validation of new single use models.

To further clarify this, a summary of benefits of increased use of multi-use disease models is given. The perspective taken is that of an HTA agency applying multi-use disease models for health care assessment intended to support reimbursement decisions, clinical guideline writing, and evaluations of current care. Getting back to our introduction (section 1.1) and the challenges identified for current policy management of the basic package, Table 11 below describes how multi-use disease models address these.

In addition to showing these advantages, the implementation of multi-use disease models will reduce the amount of time needed for each separate review by the HTA agency and external reviewers during assessments of specific treatments, while also broadening the scope of treatments that may be evaluated for health economic consequences, by allowing more opportunities to the HTA agency to perform independent evaluations. As apparent from Table 11, multi-use disease models will enhance consistency in the evidence concerning cost-effectiveness and concerning budgetary impact to support (a broader range of) decisions within disease areas and improve validity of model results, with models being more elaborately tested and used.
Most importantly, implementation of multi-use disease models puts the HTA agency in the lead and enhances the options for better integration of evaluations for reimbursement purposes with each other (more consistency) and with other related policy, like clinical guideline development and evaluations targeting an entire disease/several related disorders as part of the program for appropriate care.

Table 11 Challenges in management of the basic package and how multi-use
disease models may address these

Type of challenge	Challenge	How multi-use models address this challenge
Organizational	Stakeholders involved late	HTA agency able to require developers of multi-use models to actively involve stakeholders.
	Conflict of Interest model developers	A multi-use model by its nature is less vulnerable to this, since its applications are not all identified during model development. Furthermore, depending on choice of business case, conflicts of interests will be less prominent, especially for ownerships A, C, and D.
	New process started for each medication/treatment.	This is clearly mitigated by multi-use models, improving efficiency and consistency.
	Not aligned with clinical guidelines	When the multi-use model would include local evidence, partly mitigated. Further alignment could be obtained by including disease model analyses in clinical guideline development.
	Role HTA agency is reactive	Will be more active, as outlined in the business cases.
Methodological	International setting	This could be handled by requirements for the multi-use disease model. More worthwhile when model is repeatedly applied.
	Model structure hard to adapt	Probably less need to adapt the structure of the multi-use disease model, because its developed to be flexible enough to accommodate multiple applications.
	Oversimplified models	Repeated use renders considerate model development more rewarding, while application by parties not directly involved in model development will ensure critical review.
	Limited uncertainty analysis and model validation	More resources could be spent on this, provided the multi-use disease models are developed carefully and sufficiently funded.
	Ignore interconnections between treatments.	Multi-use disease models should account for these effects over their scope/the disease trajectory that they cover.
	Disregarding or incorrectly modelling adverse events and comorbidities.	Provided the multi-use disease models are developed carefully and sufficiently funded, involve stakeholders, and are more thoroughly validated they hold lower risk for this.
	Lack of transparency	For multi-use disease models, investment in sufficient transparency is more rewarding, since the model will be repeatedly used. Also over time, experience with the model will grow.

3.3.2 Terminology and definition

Our definition of multi-use disease models resulting from the panel
surveys was adjusted based on comments from our scientific advisors
and discussion with ZIN and the team members. Also we have added a
list of characteristics that the panel identified as helpful to separate a
multi-use disease model from a single use model. It is very tempting to

stretch the definition and consider each health economic decision model as a (potential) multi-use model, as we discovered while working on this report and discussing the various definitions provided. At the same time, it is also tempting to lean towards the other extreme of very ambitious whole disease models, with the disadvantage of high requirements in terms of upfront investments, maintenance costs and reduced options to build on existing disease models.

Our current definition is hence an attempt to strike a balance between these two extremes, while keeping in mind the intended applications as discussed with the HTA agency during our meetings:

"A health economic decision model that properly represents (part of) the dynamics of a disease trajectory to accommodate the evaluation of a range of alternative health technologies for the management of this disease. When several disease stages are included, consistent comparisons over these stages are possible."

This definition is further clarified by the characteristics that the panel elicited as important to distinguish a multi-use disease model from a "standard" health economic decision model:

- It is suitable to inform multiple policy decisions, possibly after adaptations.
- When intended for use in budgetary impact analyses: It enables projections of policy scenarios, based on setting specific epidemiological parameters.
- When intended for use in reimbursement decisions, budgetary impact analyses, clinical guidelines and appropriate care programs: It supports evidence based health care policy regarding a specific condition, and is hence setting specific, that is, based on local data where necessary.
- When intended for use in clinical guidelines and appropriate care programs: when only part of the dynamics of a disease trajectory is represented, this part is sufficiently long to cover the scope of the guideline/appropriate care program.
- It enables the evaluation of a range of health technologies, at least all alternative technologies for a certain decision point.
- When intended for use in evaluations of treatment strategies consisting of consecutive steps or treatment lines: It accounts for interdependencies over decision nodes.

This definition and list of characteristics help to separate a multi-use disease model from a single use model. Multi-use disease models may however have varying levels of comprehensiveness. For some applications, it may be desirable and feasible to develop an extensive and completely finished model with multiple decision points, a broad range of outcomes and costs (health and other), and all parameter estimates available (perhaps even linked to patient registries for regular updates). For other applications, a less extensive, but still completely finished model might do, or even a set of mandatory model components (for example concerning costing parameters, the core risk engine for a patient level model, or the most important model states and their care as usual transitions for a state-transition model). Such partial solutions may help to gradually introduce multi-use disease modelling in an

efficient way and already overcome issues with inconsistencies across assessments and issues with technical validation.

To clarify the application of multi-use disease models below we describe potential applications, taking into account the different business cases and specific levels of comprehensiveness.

3.3.3 *Potential applications*

Multi-use disease models have several potential applications. Once a multi-use model has been developed, it is quite efficient to apply it widely and not only in support of reimbursement decisions. However some applications bring additional requirements in terms of model structure and input data (see 3.3.1 above).

Several attempts have been made to produce an inventory of existing multi-use disease models suitable for application in the Netherlands. However, without a clear definition of a multi-use disease model, and criteria for its applicability for use in a Dutch setting, such an inventory is easily resulting in a mix of very diverse models. The current blueprint provides a clear definition as well as a list of possible criteria, (in section 3.3.1), that may serve as a starting point for a more clearly defined inventory. Instead of developing an inventory of existing models, it is however more effective to start drafting a list of diseases for which a multi-use disease model can be useful. In a next step, an existing local model could be identified, or, if such a model lacks, existing international models could be sought, which would have to be transferred to the local setting. When both of these are not available, a new model needs to be developed.

A multi-use disease model is not needed for every disease area, but may be very useful for diseases with a high expected number of new future interventions or diseases with a high burden in terms of costs and health losses. Criteria to select disorders/conditions that would benefit from having a multi-use disease model available may hence be based on:

- Prevalence and incidence of the disease
- Burden of disease in terms of costs and heath losses
- Number of interventions available
- Expected number of future interventions available
- Complexity of treatment pathways, that is, clear interdependencies of interventions, for instance consecutive treatment lines as in cancer treatment, or options for prevention at different stages of the disease trajectory.
- Expected number of future assessments
- Expectations concerning clinical guideline development

Such a list of diseases could be further guided by the priorities of various ongoing policy programs: both the "horizonscan geneesmiddelen", the agenda for the program for appropriate care "Zinnige Zorg", the list of clinical guidelines in need of revision, the priority list for "Beter niet doen", the projects under research in "voorwaardelijke toelating" and "grote trials", the combined ZIN/ZONMW program "Veelbelovende Zorg", as well as other research programs at ZonMw may be explored for priorities. This is outside of the scope of the current project.

A list of potential applications have been discussed with the expert panel, and they prioritized four of them:

1. Economic evaluations are the most prominent application area of multi-use disease models, in particular, cost-effectiveness analyses of treatment strategies supporting reimbursement decisions. Multi-use disease models will improve consistency among decisions on various treatments for the same disease area. Also they will enable to engage in an overall evaluation of several treatments for one disease. Examples of the latter can be found in the multiple technology appraisals at NICE.[87]

2. Next to this, support of clinical guideline development is a very attractive application of multi-use disease models. Internationally, in the UK, Canada and Australia, economic evaluation involving model analyses is an integral part of guideline development. Multi-use models are quite appropriate here, since they cover various disease stages.

3. Third, multi-use models can be applied in budget impact analyses, provided that the population modelled covers the total patient population under consideration, that is, sufficient information on disease incidence and prevalence, and on population characteristics is included in the multi-use disease model.

4. Finally, and specific to the Dutch situation, the program for appropriate care, "Zinnige Zorg" could be supported with the help of multi-use disease models, much in the same way as these models support clinical guideline development. Projection of future disease prevalence numbers could be instrumental for this program, as well as insights into the future disease burden and what subgroups of patients would be most affected in terms of costs of care and quality of life. As such the models may even help to identify unmet needs and directions for future research.

The type of potential applications will partly guide the choice among the various business cases, as well as certain methodological choices. If the HTA agency envisions to apply multi-use disease models for budget impact analyses and projections of future disease burden, then the inclusion of sufficient information about disease epidemiology becomes important, as well as the completeness and representativeness of modelling the costs and quality of life outcomes in care as usual. When most focus would be on use for reimbursement purposes, consistency among various applications and model validity for comparing treatment scenarios are more relevant than proper data on the size of the complete patient population. Building multi-use models with a modular approach would be a possible way to address the various methodological requirements needed to use the model for these multiple applications. Regarding ownership, the more frequently a multi-use disease model will be applied, the less attractive it will be to have the model owned exclusively by an external partner (that is, either commercial or not-for profit ownership, (B/E)). The total license fee requirements may be high and transparency and flexibility requirements may not be sufficient when applied for many different cases.

3.3.4   *Local relevance versus international transferability*
For multi-use disease models to be useful to the local setting, input data need to be as up to date as possible and relevant to the local context. For part of the model parameters international and/or experimental data are quite useful, and could often be obtained from published sources. However local and observational data on costs as well as on certain crucial disease parameters would greatly improve external validity. A hierarchy of evidence table (for instance [88]) helps to determine good quality sources for each input parameter in relation to intended applications.

When meant for budget impact analyses and projections of future disease burden, sufficient and up to date observational data on epidemiology (for instance disease incidence or disease progression) are needed. The existence of local good quality patient registries, concerning diseases that would benefit from a multi-use disease model, is certainly desirable, especially to inform on disease costs, current treatment practice and its possible impact on disease progression. Any models that would be adapted or newly developed would need access to these data to enable an up to date model that is representative of the decision context.

While multi-use disease models would have to be relevant for the decision context, a model that is properly divided into modules could be transferred to other settings. At the European level, the increasing cooperation in HTA dossiers could be supported by the presence of multi-use disease models, that are adjusted by applying local costing and treatment modules, as well as local disease epidemiology. This may increase the range of diseases for which it is beneficial to invest in a multi-use disease model, since the model could be applied in several countries and hence be more intensively used.

3.3.5   *Organizational and methodological topics in relation to business cases.*
Summary of organizational topics
Organizational aspects will be more or less important and new depending on the business case chosen. Experience exists in practice with both commercial ownership (B), open source modelling (C) and ownership by not for-profit research groups (E).
Mandatory use is not compatible with all business cases, so if this is required, open source (C), or third party only ownership (B,E) cannot be chosen. Liability in contrast must and can be organized in all business cases. Funding for model development, user support and maintenance similarly are needed and the best way to organize this may vary depending on the chosen business case. In case of commercial ownership (B), and to a smaller degree ownership by not-for profit research groups (E), risks exist concerning availability and maintenance. For open source modelling (C), prevention of misuse and maintenance is difficult to ensure.
For all other organizational aspects solutions can be thought off in all business cases, though they will vary per business case and may have different financial consequences for the HTA agency.

Summary of methodological issues
Some methodological issues will be more prominent depending on the chosen business case. For any of them, workable solutions to deal with most issues can be found. Options B (commercial ownership) and C (open source modelling) seem to bring some methodological risks. In case of commercial ownership, these risks concern the lack of transparency and access control. In case of open-source models, these risks relate to validity, transferability, possible privacy issues of input data, and user support.

Weighting advantages and disadvantages of various business cases
In the end, a choice has to be made by the HTA agency. Weighing all aspects, according to the team, business cases A (HTA-agency ownership) and D (cooperative ownership) seem most suitable for applying multi-use disease models as part of reimbursement assessment procedures, both ensuring some control for the HTA agency. Option A (HTA-agency ownership) would however require large financial investments, when starting with several diseases and complete multi-use models. Maybe a more feasible way to start would be to require specific modules to be standardised, adaptable, and re-usable. These could be disease specific or general. An example of the latter is the PAID tool, which provides estimates for unrelated medical costs that can be incorporated in health economic decision models. Cooperative ownership (D) has the advantage that less investments in capacity by the HTA agency are required, existing expertise is utilized and a stock of multi-use models could be developed gradually over time, if cooperation between the HTA agency and their partners is successful. However our advisors highlighted the need for incentives to ensure that especially academic research groups would be interested in such cooperation for their existing models. For instance, funding for and appreciation of the knowledge valorisation activity by the research group.
Current practice is mostly organized according to B (commercial ownership), C (open source) or E (research group as owner), that is existing multi-use models were either developed and owned by consultancy firms, or by academic groups or other not for-profit research groups, or one of the latter two groups has developed the model and made it open source. Full, free access (C, open source model) is attractive and might allow to organize FAIR access to the model. However, it also brings risks, since the HTA agency may have little influence on model validation, control over access, model maintenance, and use of the model, though they might theoretically finance someone to organize this. For B (commercial ownership) and E (research group as owner), a clear owner implies that agreements can be made regarding maintenance and liability.

3.3.6   *Conclusion*
In summary, the introduction of multi-use disease models offers several potential advantages, both organizational (consistency of decision support, initiative for HTA agency) and methodological (increased transparency and validity of the health economic decision models applied). However, challenges exist concerning the development, maintenance, and access to multi-use disease models. These can be

addressed by choosing a viable business case and ensuring sufficient resources to carry it out.

As a starting point, priorities would have to be set based on a list of disease areas that would benefit from a multi-use disease model, rather than starting with a coincidental inventory of existing models. The successful introduction of multi-use disease models could be further enhanced by careful alignment with ongoing work in registries and with European cooperation initiatives. Multi-use models strengthen the position of HTA agencies: instead of being in a position to criticize and review models developed by third parties, the HTA agency could initiate its own model-based analyses and be a (co-)developer of the models used to inform policy decisions.

4   Casus Diabetes Mellitus

4.1   Introduction

4.1.1   *Diabetes Mellitus*

Diabetes is a disorder where the body is unable to regulate the level of sugar in the blood. This causes a range of problems such as damage to small vessels in the eyes, limbs, and kidneys, resulting in retinopathy, ulcers, and renal problems. Furthermore sudden unexpectedly high or low levels of blood glucose (hypers and hypos) can appear with effects ranging from impact on mood, cognition and energy level, to damage to larger vessels and an increased risk for stroke, myocardial infarction and heart failure.[89] In Diabetes Type 1 malfunctioning of sugar level regulation is caused by a lack of insulin production due to autoimmune reactions having damaged the isles of Langerhans. Diabetes Type 2 implies that the body has become insensitive to insulin (insulin resistant), while over time the need for increased insulin production resulting from this will cause malfunctioning of the isles of Langerhans and lower insulin production. More recently, the strict subdivision has been challenged and Diabetes is nowadays seen as a continuum of disorders with varying roles of insulin deficiency and insulin resistance.[90]

4.1.2   *MICADO-R in relation to Diabetes Models in general*

Many health economic evaluation models for Diabetes have been developed. Several published reviews provide an overview of these,[91-95] and an inventory of models can be found at the registry on the website of the Mounthood diabetes challenge network. (www.mthooddiabeteschallenge.com/registry) Examples of some diabetes health economic evaluation models (hereafter briefly called diabetes models) were also briefly mentioned in 2.2.1 above. Most recent models are structured as patient level state transition models, while some cohort level models are also in use. In the current report, we briefly describe MICADO-R, an update and extension of the MICADO 2010 model coded in R.[85] A full technical documentation is provided in a separate model manual. MICADO-R is a patient level model, enabling subgroup specific analyses based on for instance age and lifestyle characteristics. In contrast to many other diabetes models, it enables evaluation of preventive interventions aiming to prevent the healthy population from developing diabetes, as well as interventions for patients with diagnosed diabetes. This enhances the evaluation of lifestyle interventions and other preventive treatments. MICADO-R is not suitable for the evaluation of diabetes screening interventions, since it does not explicitly model prediabetes as a separate state, or keeps track of HbA1c in individuals without a diagnosis of diabetes. The current description focuses on the structure of the model and the input data that were used to estimate model parameters.

4.1.3   *Outline of the current chapter*

While the separate manual will describe the model in full detail, in the current chapter we will first briefly describe the model (section 4.2) and then more elaborately the modelling process, with a focus on lessons

learnt regarding development and application of a multi-use disease model. Hence, the rest of the chapter is structured as follows. Organizational issues are discussed briefly in section 4.3. In section 4.4 we discuss the methodological issues and how these were dealt with in the current case study. New methodological issues, not highlighted by the panel are also discussed.

4.2 MICADO-R general outline

The former MICADO model was developed for the simulation of the course of disease in both diabetes patients and the general population, but did not allow to run the models for both groups integrated.[32] Its basic structure is that of a dynamic population model, with a cohort of adult Dutch diabetes patients, with or without inflow of new individuals, being followed over annual time cycles.[96] Figure 9 below shows the general structure. The model links levels of risk factors, such as BMI and HbA1C, to incidence of diabetes and to micro- and macrovascular complications. Outcomes in terms of quality adjusted life years (QALYs), mortality (life years), and costs are calculated based on disease progression and complications. Transition rates between risk factor categories and disease incidence rates depend on age, gender and risk factor categories. The current MICADO-R version describes the time-dependent changes of individuals over model states, i.e. risk factor states (e.g. BMI categories), disease states (yes/no), and for individuals with diabetes also microvascular disease severity states for three microvascular complications. Microvascular complications modelled are diabetic foot, nephropathy and retinopathy, macrovascular complications modelled are AMI, other CHD, CVA, and CHF.
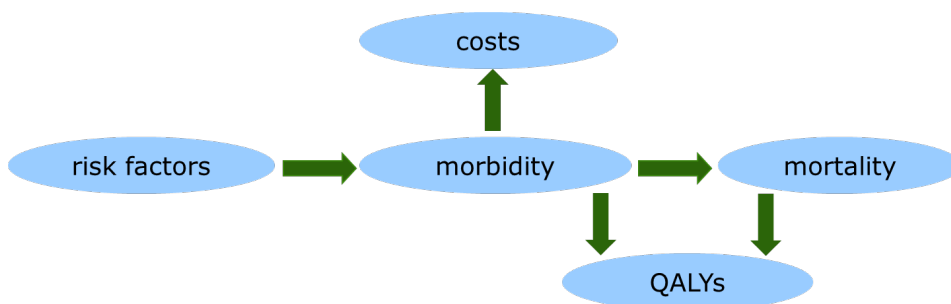

Figure 5 General structure of MICADO-R

4.2.1 Input data, previous model versions and software
Table 12 provides an overview of the main sources of model input data. Being based on Dutch GP registry data, as well as other population-wide data sources, MICADO-R covers a mixed diabetes population of mainly type 2 diabetes patients.
The first version of MICADO had 2003 as its base year and was intended to evaluate integrated care for diabetes. (Hence MICADO: Modelling Integrated Care for Diabetes) It was validated for both microvascular and macrovascular endpoints.[32] This model was implemented in Mathematica and had a cohort level structure. This version was applied for the Mounthood 2014 and 2016 challenges.[29] A model update was performed in 2013, resulting in a version with base year 2007, implemented in Mathematica. This version has been applied for the Mounthood 2018 challenges.

For the current application, MICADO was transferred to R (named MICADO-R), to enhance accessibility of the software and to enable building a user interface in R shiny [97]. The core simulation module was adjusted to enable patient level simulation. Adjustments were made to accommodate a wider range of scenarios and to enable simulating specific subgroups. The base year of the current application is 2009.

4.2.2   *Modular approach*
MICADO was developed as a "daughter" of the RIVM Chronic Disease Model and shares many of its structural characteristics with this model.[19] Like the Chronic Disease Model, MICADO-R was developed following the modular approach, and the main modules are shown in Figure 10.
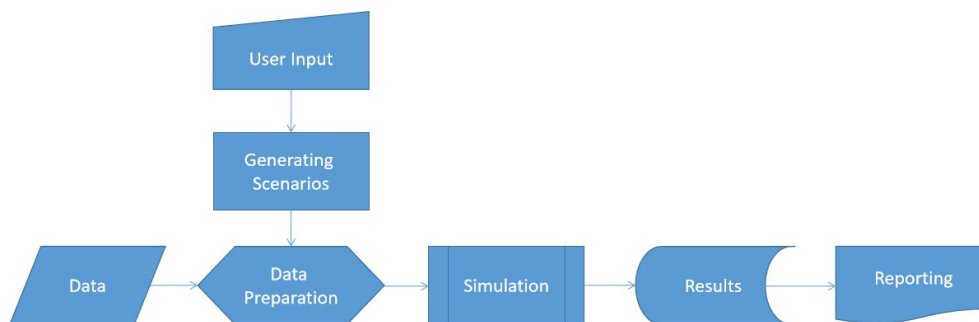

Figure 6 Modular approach of MICADO-R

The Data module contains data files storing all model parameters, i.e. distribution of risk factors, transition probabilities, etc. It facilitates easy update of the input data. In general, this module only needs updating if data input is updated.
The User Input module allows users through the user interface to select population groups (e.g. age, risk factor class, etc.), and create the scenarios they want to evaluate. See Section 3.3.1 Scenarios.
The Generating Scenarios module translates the scenarios from the user input into model parameters.
The Data Preparation module reads in all data files into lists in R, and then replaces the original model parameters with specified parameters based on user defined scenarios. Next it further transforms the data into the correct format for simulation.
The Simulation module is the core of the model, it runs the simulation based on the Data and User Input modules and calculates all outcomes.
The Results module stores the outcomes of the simulation in lists.
Finally, the Reporting module presents outcomes in tables and graphs in the user interface.

Table 12 Input data and data source

Input data	Date	Source
Population		
Population numbers	2012	CBS
Riskfactor Prevalence		
BMI	2009	NL de Maat + LASA
cholesterol	2009	NL de Maat + LASA
SBP	2009	NL de Maat + LASA
HbA1c in patients with diabetes	2019	West-Friesland (DCS)
Smoking	2011	STIVORO + Trimbos Peilstation
Riskfactor Transitions		
BMI	2010	Based on Riskfactor Prevalence
cholesterol	2010	Based on Riskfactor Prevalence
SBP	2010	Based on Riskfactor Prevalence
HbA1c diabetes	2019	Based on Riskfactor Prevalence
Smoking	2011	Based on Riskfactor Prevalence
Disease Prevalence and incidence, excess mortality and case fatality		
Diabetes	2011	LINH+LMR
AMI	2011	LINH+LMR
CVA	2011	LINH+LMR
CHF	2011	LINH+LMR

4.3 Lessons learnt concerning organizational issues.

The current model development project was a case study and as such organizational embedding was relatively straightforward, with the model development being part of the ZIN tendered project. The ownership of model code will follow business case D (Academic cooperation scenario with shared ownership by HTA agency+research group), which in this case will be the shared ownership of MICADO-R by a research institution (RIVM) and an HTA agency (ZIN), together with an academic partner (AmsterdamUMC). The shared ownership allows for financing of further development, updating and hosting by public funding and research grants as well as licensing. Agreements will have to be made regarding division of these funds. Furthermore, possible issues regarding fair competition between model suppliers will be applicable here.

In case ZIN decides in the future to have the MICADO-R model mandatory for reimbursement decision regarding for instance diabetes medication, misuse should be prevented and clear terms and conditions of model use should be specified to waive liability in case of misuse.

Other issues identified concerning organization were less relevant for this specific case study because of its development in an existing cooperation between the RIVM and academia. Stakeholders for MICADO-R would be clinicians involved in diabetes care, individuals with diabetes, policy makers and industry. Pragmatically, an existing gremium, the "round table for diabetes" (ronde tafel diabetes) was chosen to access

these stakeholders. They helped to clarify the priorities concerning scenarios, and steered model development to focus on accommodating scenarios regarding lifestyle interventions as well as regarding new types of oral antidiabetics like SGLT2 inhibitors.

While ideally stakeholders would have been involved intensively during the model development process and hence should have also had a say in structuring the model and indicating input data sources, this was in practice hardly feasible. Reasons were: a. the existence of a previous version of the model, and hence current structural choices being limited, b. limited resources/time on the side of the model development team, c. lack of interest/incentives on the side of the stakeholders, and d. the exceptional circumstances of Spring 2020 with the Corona-pandemic resulting in specific regulation being in place. Once a clear role for multi-use disease models has been established, lack of interest from the side of stakeholders will probably be less of an issue. For model developers sufficient time and resources need to be budgeted to include stakeholder consultation in a systematic way and to take the time needed to also adapt choices to stakeholder input.

Recommendations
1. Stakeholder involvement should be timely and cover all relevant stakeholders, not just clinicians. Lack of interest from the side of stakeholders to participate in stakeholder consultation rounds could be solved either by offering proper payment, or -better- by ensuring clear communication regarding the later application of the model, so stakeholders can be informed regarding the purpose of contributing to model development.
2. Schedule at least 24 months for model development and validation irrespective of pre-existing models, to allow for appropriate input data selection, model validation and stakeholder consultation.
3. Stakeholders tend to have relatively little attention for limitations in terms of time and budget. Hence the team advises to offer stakeholder closed rather than open choices. To avoid too much steering by the model developers, this could be organized by consultation in two rounds. While the first round elicits for instance relevant scenarios, the second round asks for priorities and a preset number of scenarios.

Concerning software, many options, such as the use of Shiny in R, are currently available to make model application easier for the stakeholders involved. However, these options are relatively new and their development requires a certain degree of programming expertise. Additionally, the interface has to be intuitive for the user, which requires skills on the side of the model development team. The advantage of R Shiny is that the model can be run either completely on site, or through a web based interface. In the first situation, the model applicants need access to R. In sum, to develop a model that can easily be applied by external users, additional expertise and time are required for programming and communicating an intuitive interface.

4.4 Lessons learnt concerning methodological issues.

4.4.1 Model development (section 3.1.4, topics 7 to 9)

Given the relatively limited time of 11 months available for model development, the current MICADO case study was selected because an existing model could be updated and extended. The team proposed three existing models for actualization, this being the only way to perform a case study of multi-use disease model development within this time frame. The diabetes application was chosen, since it would present a case study sufficiently different from a previous case study in advanced prostate cancer. Researchers in both case studies felt that time was limited, which stressed that a sufficiently long time horizon is advised for future multi-use disease model development projects. This will enhance the ability to involve stakeholders (see also topic 4 in section 3.1.3) and to select and obtain additional appropriate sources for input data. Such processes take time, especially since external parties involved need to be approached and meetings scheduled. Hence our second recommendation is reinforced

> ### Recommendation
> 2. Schedule at least 24 months for model development and validation irrespective of pre-existing models, to allow for appropriate input data selection, model validation and stakeholder consultation.

Topic 7: Modular approach

The MICADO-R version was developed in a modular way, like its predecessors the RIVM Chronic Disease Model and the MICADO 2010 model. Each module was written and stored in a separate R routine, allowing clear "bookkeeping" of input and output variables for each module and linkages between modules.

The communication between the shiny interface and the R code itself, and especially within the shiny interface (when input values provided by the user will determine the next steps in the shiny interface) was quite a challenge.

An additional advantage of this modular approach, and more specifically, the way this was implemented in the RIVM Chronic Disease Model and in MICADO, is that it is relatively easy to run the model for a different selection of diseases or risk factors, without altering the complete model.

A disadvantage was that the model structure was not so easily grasped by new model developers, who needed time to get acquainted with the model code.

> ### Recommendation
> 4. Use a modular structure for most multi-use disease models, unless good reasons exist to deviate from this, or the disease dynamics to be modelled are relatively straightforward.
> 5. Ensure elaborate technical documentation, and enough capacity, so that new model developers can get introduced into existing models.

Topic 8: Model complexity
Diabetes is quite a complex disorder to model, since it has a large number of complications and comorbidities. Several existing diabetes models are more complex than MICADO-R, for instance regarding keeping track of prediabetes and/or glycemic levels in non-diagnosed individuals, regarding hypoglycemia and hyperglycemia, or regarding the inclusion of comorbidities like dementia and depression.[92, 93] On the other hand, the current model has a broader scope, with also the healthy population and incidence of diabetes being modelled. Models for type 1 diabetes cover a different patient population, and have a somewhat different structure as well.[98]
The current model is as such a compromise with the focus on representativeness for the Dutch population and consistent evaluation of interventions along the progression path from healthy, but with increased BMI to complicated diabetes. The choice of level of detail was also steered by two pre-selected scenarios for evaluation, being lifestyle interventions and new medications for subgroups in type 2 diabetes. For instance, the requirements for the evaluation of new medications included possibility to evaluate scenarios in subgroups, and the option to include treatment effect not just through the intermediate risk factors (glycemic level), but also directly on the incidence of complications (reduced incidence of stroke) and mortality. During the process of model development we kept track of essential requirements, nice to haves, and a wishlist for future improvements.
Another issue was the modelling of risk factors, which could be done continuously or discretely (in risk factor categories). The latter option seems mathematically attractive since it generates a discrete-state transition model. However, the number of multivariate model states grows exponentially, and this turned out to be a serious practical problem. So, for future model developments continuously distributed risk factors are more attractive.
Meetings with ZIN and other stakeholders (diabetes round table) served to select intervention scenarios. The team experienced that during these meetings it is easy to draw up a long list of desirable properties, but quite difficult to obtain priorities. It is important to stress the inherent limitations of previous choices and limited time and funds, while the current model version will have a list of topics for further improvement.

Recommendation
6. Start each model development process with several meetings with stakeholders and the HTA agency to get a clear idea of required applications and desirable future options for applications. The final selection has to be done by the model owner and model commissioner, hence will depend on the business case chosen. We recommend however the close involvement of the model development team. Inherently choices have financial and development time implications and are also dependent on the availability of appropriate data.

Topic 9: The role of Empty shell models
No empty shell code was applied for the current case study, since the model developers built on the available coding for the RIVM chronic disease model.

4.4.2   *Input data*

As part of the case study, contacts with two important sources of diabetes data had been established prior to the start of the project.[99, 100] In addition, during the project, it was initiated to obtain quality of life measurements from the Maastricht study.[101] Further sources of input data were presented in Table 11 above.

Topic 10: Access to patient level data, especially on effectiveness.

During the case study no patient level data on effectiveness were used, effectiveness information was obtained from published sources. While obtaining other input data we ran into the issue that standard data request formats were geared towards use for single research questions resulting in one or two publications. In contrast, we need the data to estimate a model parameter, which will be applied in the model repeatedly and might then require maintenance (updates) and would not directly result in a clear publication regarding this specific model parameter. We solved this by proposing to try and publish the work related to this model parameter. Nevertheless this process took a lot of time and hence in the end, the published data were used.

Recommendation

7. Access to patient level data sources has to be organized timely and data requests are often not suitable for use in models. The support of the HTA Agency could be instrumental in this.

Topic 11: Compatibility with GPRD

No such issues were encountered when working on the case study, reinforcing the team's impression that this is the exception, not the rule, since model development is usually based on secondary data sources.

4.4.3   *Validation and Transparency*

To enhance model transparency, during the development we communicated about our choices with the HTA Agency. Also we organized a workshop to explain the final model to a group of prospective model users.

We planned as well to organize several meetings with stakeholders. This was pragmatically arranged by contacting the "Ronde tafel Diabetes", an existing platform for stakeholders in the area of Diabetes. Only a single meeting actually took place, partly this could be explained by the special circumstances (lock-down policies) in place during spring 2020. Partly, this also had to do with the model development process being an update of an existing model, hence the need to carefully check the model structure with stakeholders was less than would be the case for an entirely de novo multi-use disease model. This brings of course the drawback that previous choices would go uncriticized.

Regarding uncertainty analysis and validation, several options exist, but time and resource limitations imply that these ended up on our Wishlist for future research.

Topic 12: Uncertainty analysis, Model validation and Transparency

Lessons learned from our case study concerning these three topics can be summarized simply by the need to set aside sufficient time and

resources to address these topics properly. We intend to apply a careful uncertainty analysis, with the help of the TRUST tool, use the AdViSHE tool to report on model validity tests performed and write a clear model manual with transparent reporting of the model structure, input data analyses, and model coding assumptions.

Recommendations
8. Proper attention for uncertainty analysis, model validation and transparency is essential and will sufficient time and resources.
9. Transparent communication about the model and organizing stakeholder involvement may require a multidisciplinary team with other competences than strictly modelling expertise.

4.4.4   Model use
Our case study included the delivery of a Shiny interface to enable model users to concentrate on scenario definition and enhance user friendliness for external users. Such an interface allows to apply the model in two modes: either by actually obtaining all model code and running the model on site. Or by web based access, through a link to the Shiny interface, while the model runs on a server.

Topic 13: Transferability.
No specific challenges were encountered during our case study concerning model transferability, since the model was developed for the Dutch population, which is also the setting in which it will be applied. No recommendations needed to be formulated concerning this topic.

Topic 14: Access for users (practical)
As mentioned above, practically access was organized through a Shiny app, which is a specific software system suitable for use in combination with models programmed in R. More information on this can for instance be found in [97]. Experience with the model users learned that several rounds of testing are required to develop an intuitive interface that is suitable to users other than people with a lot of modelling expertise.

Recommendation
10. A user interface, suitable for the model software is in general recommendable. Depending on level of access, more technical/advanced options can be made available. A case study with stakeholder involvement to test the intuitiveness of the interface is recommended as it may overcome later difficulties in model application.

Topic 15: Limits to acceptable run time/software
Actually model run time turned out to be problematic during the development phase of this case study, and several coding solutions had to be considered to solve this issue. Given that uncertainty analyses would have to be added, which increase run times easily by a factor of 100-1000, we considered acceptable run times for a single simulation would be in the order of magnitude of (tens of) minutes, not hours or days. The model's cohort-level version is available as an alternative and fast solution with very short run times, to get a first impression on scenario outcomes.

> **Recommendation**
> 11. Clear communication with the model users concerning acceptable model run time is advised. Sometimes a back-up simple alternative model can help to sort out the scenarios that are worth further investigation at a shorter run-time.

4.4.5   *Model results*

Model results in our case study are made available to the model user through the interface. Based on user feedback, we included a log function and allowed to report results from this interface.

Topic 16: Governance for access to model results.

For the current case study, access to model results will be organized relatively straightforward, since we do not expect any governance issues for our scenarios. However, the way access is organized through a user interface would allow that the user provides confidential input to a web based interface, which is then transferred to the server that runs the actual model. In that case, IT experts would need to be involved to ensure safe transfer of confidential data between the interface and the actual model.

Topic 17: Improve model understanding (explanation).

The results in the Shiny interface are presented in graphs and tables. A workshop is organized to explain in person and in sufficient detail the interpretation of the model output.

> **Recommendation**
> 12. Different model users, for different applications will be interested in different (intermediate) outcomes. Hence the model should be able to show a wide range of outcomes, of a which a selection can be made through the interface.

4.4.6   *Model maintenance*

For the case study, model development was the core topic, however future maintenance of course also deserves attention. Ensuring future model maintenance is a matter of a careful design that enhances maintenance as well as sufficient resources set aside for this, for instance a fixed annual budget set aside for the model model developers to ensure maintenance. Be aware that even keeping the model running with new versions of R may need model maintenance.

> **Recommendation**
> 13. Reserve budget and time for model maintenance and plan this for a period ahead. Start for instance with 120 hours annually to mend minor (technical software) issues, ensure updates of easily updatable parameters and keep track of the need for major updates once new data is available.

Topic 18: Need for official updates

Since the model ownership as of yet is clearly defined as a joint ownership by RIVM and AmsterdamUMC, model releases have been provided by the RIVM and were labelled by the year of release as MICADO 2010 and MICADO 2013. The current new version will be labelled MICADO-R. A full and complete model version was stored in the

RIVM servers to serve as a back-up copy of the official version. It turned out that in actual use, for instance to participate in the MountHood Diabetes challenges minor adaptations to these official copies have been made in the past, without a clear trace.

Recommendation

14. Use good repository systems, e.g. GIT, to keep track of versions and official updates, especially when the model code is shared with model users and stored at several locations. At the very least, store a back-up complete copy for reference.

Topic 19: Sustainable knowledge base

Knowledge on the previous MICADO versions in the past was kept alive by ensuring sufficient research funding for model based analyses on diabetes. This was at times a hard task, and no continuity was guaranteed. The knowledge base was relatively small and consisted of 3 individuals. During our case study this turned out to be a minor problem, since 2 of these 3 individuals were involved in the current project. However if circumstances had been different, the problem would have been larger.

The only way to ensure a sustainable knowledge base is to ensure continuity in model applications, which may be easier to accomplish in cooperation with a HTA agency. But even then, the future of new treatments is somewhat unpredictable. Having elaborate documentation and clear manuals is essential and reduce the need for in person explanation.

Recommendation

15. Enough time and resources need to be planned during model development for proper and elaborate documentation, both in the model code, and on the model code, the mathematical and epidemiological theory behind it, and its applications. The team recommends to include a 15% extra time for this purpose in the model development phase and to set aside 2 weeks annually for model documentation maintenance.

Topic 20: Adaptability of model and approval of adaptations

The current MICADO-R version is developed in a modular way. However modules are closely linked and adaptations in the model require knowledge of the underlying model structure. We encountered for instance the issue that the model works with a reference scenario which in all code is presumed to be scenario no 1. Any changes in this order would require careful code checking. On the other hand, several other aspects of the model have been pre coded to be flexible to adaptations, for instance adding new complications, new risk factors or new age categories would run rather smoothly. For the scenarios and the user interface, we discussed upfront what type of scenario we expected and tried to develop a flexible input structure for these. For instance for all scenarios, an introduction period when the effect of the intervention gradually grows, a full effect period, and a waning period (when the effect of the intervention gradually declines) have been included in the interface. When not needed, these periods are simply set to 0.

Approval of adaptations has in this model development process been discussed between the developers. Future adaptations and its approval may be managed more formally by using Git.

> ### *Recommendation*
> 16. To enhance adaptability, proper coding habits have to be carefully followed. Even when more flexibility comes at a cost of more complexity, it usually pays off later, by showing more adaptability of the model. Some choices can be prefixed and hidden for users.

4.5 Further lessons learnt from the case study in diabetes mellitus.

Next to the issues already identified by the expert panel, and discussed in the blueprint, several new issues arose during the current case study. During the model development process we also experienced the importance of having a development team with sufficient expertise on the disease in question and on health economic decision modelling. This expertise is relatively rare and model builders tend to be overloaded with tasks, which might become a real restriction in some of the business cases presented. For instance for scenario A, the HTA agency needs to hire this expertise inhouse, which might be a real challenge. In contrast in scenarios B and E, the HTA agency depends on a third party to allocate sufficient expertise at the time that the agency needs it. Careful contracting may be warranted in this case, the arrangements made by NICE in the UK might serve as an example. Having these arrangements also in place at several university groups in the Netherlands has contributed to the growth of health economic modelling expertise in our country, by providing a continuity in funding.

4.6 Applicability and potential use

4.6.1 *Limitations of the current Diabetes model.*
The model allows to investigate outcomes for various subgroups for different scenarios of implementation. Thus model users can apply the model to compare various policy choices regarding treatment indication criteria.
However, full optimization within the model (so having an algorithm find the optimal combination of treatment, deciding on treatment duration by subgroup) requires very many assumptions. For instance, the precise objective should be made clear, and careful definition of constraints is needed, as well as careful definition of what exactly can be varied in the optimization. This is outside of the scope of the current project.

4.6.2 *Potential applications of the current model*
The Diabetes mellitus model as it has been released now (MICADO-R) is suitable for cost-effectiveness studies on a wide range of diabetes treatments, both lifestyle interventions and medications. It is also suitable for projections and budget impact analyses, because the default model population is representative for the Netherlands. Smaller, specific subgroups can also be evaluated, but these should be specified by the model user. That is, the model user then needs to adjust several input data files and be aware of the required file structure. Also the model has not (yet) been validated extensively for use in subgroups and applications in too small subgroups may cause biased results.

Table 13 shows the applications as identified in our blueprint and being possibly relevant and whether MICADO-R is suitable for them. The model is applicable for the most important uses as identified by the panel.

Table 13 Relevant applications for multi-use disease models, as listed by the panel, together with their panel priority and MICADO options.

Application (similar applications were combined)	Relevant for purpose of ZIN	MICADO-R suitable to perform this application
Resource allocation: Optimization of resources over a set of interrelated interventions over the entire disease pathway of interest.	Possibly	Not in its current form
Budget impact estimation: estimation of the overall costs (and health benefits) of certain policy choices for a jurisdiction, within a certain year/range of years.	Yes	Yes
Guideline development: support evidence over the costs and benefits of several interventions in a consistent way	Possibly	Yes, though not for all thinkable interventions.
Projections: provide insight in the expected numbers of patients over time.	Possibly	Yes
Compare alternative policies concerning prevention and treatment	Yes	Yes
Exploration: new treatment options/scenario analysis/subgroups (e.g. by SES)/biological mechanisms	Possibly	No
Support government investment decisions	Possibly	To some degree/Yes
Identification of key uncertainties and their potential impact	Possibly	Partly
Equity analyses: You may want to study the effect of different interventions in people with e.g. various economic status	Possibly	No
Umbrella trials (network meta-analysis type of use)	Possibly	No

5 Overall Discussion and conclusions

5.1 The prospect of applying multi-use disease models, main study findings

Multi-use disease models are a promising approach to tackle several drawbacks of working with single-use health economic models for supporting reimbursement decisions and other policies concerning the health insurance package, and the delivery of appropriate care. Multi-use disease models enhance consistency because they offer a wide applicability to several (types of) policy questions. They likely enhance model validity, transparency, involvement of stakeholders and comprehensiveness of uncertainty analysis, as well as proper documentation because multi-use implies more pay-off for efforts into better modeling.

As a result multi-use disease models, or similar concepts with other names (generic model, reference models, whole disease models), have been developed and applied in health economic decision modelling for several decades. Their application in health care policy support and more specifically in supporting decisions concerning the composition of the health insurance package has been limited, but not absent. For instance, diabetes mellitus models applied in decision support were quite often multi-use disease models. Most models used for supporting policy decisions concerning population screening programs could also be classified as multi-use disease models. On the other hand, the large majority of models that underpin the economic evaluation of new pharmaceuticals are not multi-use disease models.

As a starting point to provide a blueprint for further application of multi-use disease models in health care policy support and more specifically in supporting decisions concerning the composition of the health insurance package, this study clarified the definition of a multi-use disease model using input from a large group (N=54) of international HTA modeling experts.
"A health economic decision model that properly represents (part of) the dynamics of a disease trajectory to accommodate the evaluation of a range of alternative health technologies for the management of this disease. When several disease stages are included, consistent comparisons over these stages are possible."
This definition is further clarified by the characteristics that the panel elicited as important to distinguish a multi-use disease model from a "standard" health economic decision model:

- It is suitable to inform multiple policy decisions, possibly after adaptations.
- When intended for use in budgetary impact analyses: It enables projections of policy scenarios, based on setting specific epidemiological parameters.
- When intended for use in reimbursement decisions, budgetary impact analyses, clinical guidelines and appropriate care programs: It supports evidence based health care policy regarding a specific condition, and is hence setting specific, that is, based on local data where necessary.

- When intended for use in clinical guidelines and appropriate care programs: when only part of the dynamics of a disease trajectory is represented, this part is sufficiently long to cover the scope of the guideline/appropriate care program.
- It enables the evaluation of a range of health technologies, at least all alternative technologies for a certain decision point.
- When intended for use in evaluations of treatment strategies consisting of consecutive steps or treatment lines: It accounts for interdependencies over decision nodes.

The above definition strikes a balance between the fully comprehensive perspective of "whole disease models", and the perspective of "reference models" which would qualify any health economic decision model that serves as a standard for several assessments as a multi-use model. A list of potentially relevant applications and associated model requirements has been scrutinized by our expert panel resulting in a priority list of applications for multi-use disease models. The most important are: comparing alternative policies, and supporting resource allocation decisions. Two further potential applications were budget impact estimation, and guideline development.

Five business cases have been outlined to offer various ways in which an HTA agency, like the Dutch Healthcare Institute, could organize and implement multi-use disease models as part of health care policy support:
  A. Full HTA agency ownership
  B. Private/Commercial ownership
  C. Open source model (No single distinct owner)
  D. Academic cooperation scenario (HTA agency+ research group)
  E. Academic or other research institution is owner.

As discussed in section 3.2 each of these business cases has its advantages and disadvantages. The first decision required is between either a limited implementation for a selected number of disease areas, or a more widespread implementation of multi-use disease models. Option A likely requires substantial up-front investments by the agency, which however may pay out once multi-use disease models are used more often. Option A (full HTA agency ownerwhip), however, would require sufficient modelling capacity and expertise at the HTA agency, including a senior health economic modeller with a good knowledge of existing models in various fields to adequately organize the agency's strategy. The other options allow for more gradual implementation of multi-use models by starting cooperation with external parties for those disease areas for which a multi-use disease model is deemed relevant. In section 3.3.3 we discussed how such disease areas could be selected. International cooperation is an interesting way to divide the costs of a multi-use model among several HTA agencies and increase its efficiency. This inevitably asks for models that are easily transferable to different settings, for instance by using modular modelling techniques. To address these and other methodological issues involved, section 3.1 outlines the theoretical findings. Based on this discussion, options B (commercial ownership) and C (open source modelling) seem to bring some methodological risks. In case of commercial ownership, these risks concern the lack of transparency and access control. In case of open-

source models, these risks relate to a missing clearly identifiable owner of the model. This could imply unclear responsibilities regarding validity, transferability, safety of input data, and user support.

Based on our case study in Diabetes Mellitus, 16 recommendations were made on topics covering model development, input data, validation and transparency, model results and model maintenance (section 4.3 and 4.4). Table 14 below briefly repeats the 12 most important recommendations. In short, developing a multi-use disease model is a process that requires a multidisciplinary team and sufficient time, because of the variety of activities involved. Expertise needed covers both mathematical, epidemiological and health economic modelling knowledge, but also IT expertise and communication and organizational skills to organize stakeholder involvement and communication about the model. A user friendly interface is needed to allow external users to easily apply the model. This interface should be flexible enough to accommodate a range of different applications. Ensuring early access to input data, sufficient model development time and resources, as well as post development user support, are important.

Table 14 List of most important recommendations for multi-use models in practice.

RECOMMENDATIONS BASED ON CASE STUDY DIABETES TYPE 2.
Stakeholder involvement should be timely and cover all relevant stakeholders, not just clinicians.
Schedule at least 24 months for model development and validation.
Include priority setting in several round as part of stakeholder involvement.
Use a modular structure for most multi-use disease models, unless good reasons exist to deviate from this.
Access to patient level data sources has to be organized timely.
Proper attention for uncertainty analysis, model validation and transparency is essential and will require time and resources.
Transparent communication about the model and organizing stakeholder involvement may require a multidisciplinary team.
A user interface, suitable for the model software is in general recommendable.
The model should be able to show a wide range of outcomes.
Reserve budget and time for model maintenance and plan this for a period ahead.
Use good repository systems, e.g. GIT, to keep track of versions and official updates.
For documentation, 15% extra time is needed in the model development phase and additionally 2 weeks annually for model documentation maintenance.

The case study thus learnt how several of the methodological issues were indeed met in practice and could be dealt with. To learn more on the different business cases, a case study is less suitable since by its very nature the organizational context is based on a tendered project, with the contracting parties having existing regulations concerning ownership of deliverables. We recommend further exploration with our business cases as a starting point. For instance, the HTA agency could

approach several parties for an offer concerning model development and maintenance in a number of priority disease areas.

The expert panel likewise identified and prioritized a range of methodological and organizational issues to be addressed before implementing multi-use disease models (see Table 7). As a first observation, many issues identified by the panel actually concerned topics that any proper health economic decision model, whether intended for single or multi use, should address. Another relevant finding is that multi-use models will not be useful for all disease areas, and priority setting is required. Some flexibility may be added by varying the comprehensiveness of the multi-use part of a disease model depending on the disease area in question. That is, sometimes only a part of the model could be chosen to be multi-use, rather than the entire disease model.

5.2 More initiative for HTA agencies

Like other ongoing developments regarding the initiation of patient registries, multi-use disease models may serve to empower HTA agencies. They may take the initiative to consider for what diseases/disease areas a multi-use disease model would be helpful. This might for instance be done based on the following criteria: disease burden, complexity of treatment pathways, number of treatment options, anticipated number of new treatments that are entering the market, and anticipated assessments and new clinical guidelines. See also section 3.3.

After such priority setting, the HTA agency might, for the disease areas that were prioritized, initiate development of or access to suitable multi-use models. An inventory of existing models, and/or available datasets may support this. When a model exists, the question is whether it is valid and accessible. When a model is not accessible, the question is whether one needs to be developed, either from scratch, or based on existing models that do not yet qualify as multi-use.

Depending on the chosen business case, the agency could then develop/adapt a model themselves (A), approach third parties for model development (B,C,E), or start with a cooperative project (C,D). Also the agency may consider the option to not develop a complete model, but only identify and develop/order crucial model elements, or modules, which they could then require to be included in any health economic decision model that is applied in assessments. Finally, the agency may also decide what stakeholders should be involved and at what stage. All of this, whether implemented for a wide range of disease areas, or more selectively for specific disease areas, will help to improve the quality of advice provided by the HTA agency.

5.3 Conclusions

In summary, the current report helps to (further) implement multi-use models by identifying and discussing a range of methodological issues and by providing recommendations on how to deal with them in practice, based on a case study in Diabetes Mellitus. A number of business scenarios sketch how an HTA agency might organize the implementation and what decisions are to be taken concerning model ownership, mandatory use, licenses, model maintenance and output

storage. A list of recommendations for practice further supports model development and maintenance. This will help the Dutch Healthcare institute to determine whether and how multi-use disease models could be implemented in order to support health policy decisions.

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Supplement 1. Expert panel

Table 15 List of experts participating in the panel

Name	Affiliations
Professor Fernando Antonanzas	University of La Rioja, Spain
Nigel Armstrong, PhD	Kleijnen Systematic Reviews Ltd
Christian Asseburg, PhD, MSci	ESiOR Oy, Kuopio, Finland
Sixten Borg, PhD	Lund University and Regional Cancer Centre South, Lund, Sweden
Professor Hendriek C. Boshuizen	National Institute of Public Health and the Environment
Keith Cooper, PhD	Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, UK
Qi Cao, PhD	Guest researcher health economics, University of Groningen.
Professor Jaime Caro	McGill University, Faculty of Medicine and Health Sciences MDCM, FRCPC, FACP, Chief Scientist Evidera, Bethesda, United States London School of Economics
Professor Murray Krahn	Department of Medicine, University of Toronto
Isaac Corro Ramos, PhD	Institute for Medical Technology Assessment (iMTA)
Salah Ghabri	Haute Autorité de Santé, Paris, France
Lucas Goossens, PhD	Erasmus School of Health Policy & Management
Gimon de Graaf, PhD	Institute for Medical Technology Assessment (iMTA)
Janneke Grutters, PhD	Radboud UMC
Henk B.M. Hilderink, PhD	National Institute of Public Health and the Environment
Yawen Jiang, PhD	School of Public Health (Shenzhen), Sun Yat-sen University
Dr LM Lamers (personal views)	Dutch Ministry of Health, The Hague
Mark Lamotte, PhD	Cardiologist -Senior Principal, Global Health Economics Leader, Global HEOR/RWS, IQVIA
Professor Stefan K. Lhachimi	Institut für Public Health, University Bremen
Professor Giorgio Lorenzo Colombo	CEFAT - Center of Pharmaceuticals Economics and Medical Technologies Evaluation, University of Pavia, Italy
Suzette Matthijsse, PhD	Bresmed, Utrecht
Josephine Mauskopf, PhD, MHA,	RTI International, Research Triangle Park, North Carolina, USA
Balazs Nagy, PhD	Syreon Research Institute, Economic Modelling Division, Budapest
Professor Andrew J Palmer	1 Menzies Institute for Medical Research, The University of Tasmania, AUSTRALIA 2 Centre for Health Policy, School of Population and Global Health, The University of Melbourne, AUSTRALIA
Douwe Postmus, PhD	University Medical Center Groningen
Pedram Sendi, PhD, MDD, DDS	Insititute for Clinical Epidemiology, Basel University Hospital, Basel Switzerland
R.A.A. Vonk, PhD	Council for Health and Society (RVS)
George A.K. van Voorn, PhD	Biometris, Wageningen University & Research
Gijs van de Wetering, PhD	Pharmerit
Durk-Jouke van der Zee, PhD	Department of Operations, Faculty of Economics & Business, University of Groningen, Groningen, The Netherlands
And 24 anonymous experts	

Table 16 Characteristics of experts in both rounds

	Respondents round 1 (N=51)	Respondents round 2 (N=42)
Gender		
Male	35 (68.6%)	32 (76.2%)
Female	16 (31.4%)	10 (23.8%)
Region		
EU	47 (92.2%)	37 (88.1%)
Non-EU	4 (7.8%)	5 (11.9%)
Working Environment		
Academic	23 (45.1%)	19 (45.2%)
Consulting	12 (23.5%)	10 (23.8%)
Industry	4 (7.8%)	3 (7.1%)
Policy	12 (23.5%)	10 (23.8%)

Supplement 2. Expert panel rounds 1 and 2

Questionnaire Round 1
Disease specific models for health care policy in the Netherlands
Introduction to the project
This page shortly introduces the project and the project team.

The Dutch National Healthcare Institute has initiated the current project, to investigate disease models as a possible option to support more structured use of health economic evaluation and other applications of disease models as part of its policy advisory role. Currently health economic evaluations and other simulation model outcomes play a role in reimbursement decisions concerning drugs with added value, but less so in reimbursement decisions on non-drug treatments, in guideline development, or in the program "Zinnige zorg" (which critically evaluates all healthcare within a certain area of care, e.g. respiratory disorders, or mental health) .

The research team working with the Dutch Healthcare Institute on this project consists of the following researchers and institutions:
- Dutch National Institute for Public Health and the Environment (RIVM): Dr TL Feenstra, Dr GA De Wit; Dr A van Giessen.
- University Medical Centre Utrecht: Dr GA de Wit; Dr GJW Frederix; Dr J Wang.
- University of Twente: Dr H Koffijberg;
- Maastricht University Medical Centre: Prof Dr M Joore; Dr B Ramaekers; MSc X Pouwels
- Groningen University: Prof Dr TL Feenstra

In addition, Prof Dr Paul Tappenden (Professor of Health Economic Modelling, HEDS, ScHARR, University of Sheffield, Sheffield, UK) and Dr Hossein Afzali (Senior Lecturer, Adelaide Health and Medical Sciences , The university of Adelaide, Australia) are involved as project advisors.

The project will consist of three tasks:
1. Build and provide access to an actual disease model, by way of a model interface.
2. Investigate the methodological and structural issues involved in using disease models for health care policy support
2. Report on the findings

As part of task 2, we would like to involve a panel of international experts, which is why we approached you.

Disease modelling in support of priority setting in healthcare
This document consists of 5 pages of text, with 4 questions you are kindly asked to answer. Please feel free to add any comments you consider necessary to explain your points. Many thanks for your cooperation.

1.   Terminology and definitions
Within health economic decision modelling, models used vary strongly in their scope and hence in the width of their applicability. Some models are tailored towards a specific decision problem, while others have a more general focus.

The term "Disease model", or sometimes "whole disease model" (1) is meant to distinguish models with a broad scope and wide focus from models specifically developed to evaluate a specific intervention for a specific decision problem. So called "single use models" mostly cover just part of the disease process, part of the treatment spectrum, and/or part of the patient population.

Other terms used in this respect are "reference models" and "disease specific models" (2-4).

Next to health economic decisions, this type of models with a broad scope have been widely used to support purely epidemiological studies, and public health research. Terminology used has been "public health model", "Health impact model", and "population model" (5-7)

Some of these terms, like "disease model" seem quite vague term, while others bring strong suggestions on required completeness and use.

We will adopt the term "disease specific model" in the current document.

Tappenden et al.(1) define a "whole disease model" according to tree principles:
1: The model boundary and breadth should capture all relevant aspects of the disease and its treatment—from preclinical disease through to death; 2: The model should be developed such that the decision node is conceptually transferable across the model; 3: The costs and consequences of service elements should be structurally related.

Afzali et al.(2,3) and Frederix et al.(4) use the term "reference model", or "disease specific reference model". Such a model should represent "the knowledge and uncertainty about states/events relating to the disease progression on the basis of the best available evidence." It is to be applied to a wide set of interventions for a specific disease (e.g., drugs and procedures that may target alternative mechanisms or stages of disease).

Characteristics of a disease specific model
This is a list of characteristics as the project team has defined it based on the literature.
   1. It combines information on disease trajectories with data on demography and epidemiology

2. It covers not just a specific cohort within a patient population (e.g. men aged 60+), but an entire patient population (e.g. all patients with diabetes type 2)

2. It focuses on a conceptual model that is an acceptable representation of the condition in question to all stakeholders, rather than a conceptual model that is most suited to a certain specific decision problem.

3. It simulates disease history /patient trajectories of a certain disease. This could be a very broadly defined chronic condition like diabetes mellitus, or a more specific condition, e.g. metastatic breast cancer—here our definition deviates from Tappenden (1). Most disease models simulate individual patient trajectories, but this is not necessary. Some models simulate average patient lives.

4. Models start with the healthy population and typically cover the entire treatment spectrum from primary prevention up until palliative care (whole disease model). However, they can also cover a shorter part of the disease trajectory, as long as they are suitable for repeated use, allow evaluation of a wide range of treatments and cover a broad patient population.

5. It is developed and maintained for repeated use.

Examples of disease specific models
To help set the stage, we listed a number of models that we as a research team would consider qualify as disease specific models. This list is certainly not complete.

- The ECHO type 2 diabetes model, the UKPDS diabetes model, the CORE diabetes model, and many other type 2 and type 1 diabetes models.
- See https://www.mthooddiabeteschallenge.com/.
- Many cancer models, for instance the MISCAN colon cancer model and the SimCRC colon cancer model. See https://cisnet.cancer.gov/.
- The SIMRISK breast cancer model. See de Bock et al. (8).
- The RIVM chronic disease model and its sister, Dynamo-HIA (see https://www.dynamo-hia.eu/ and Lhachimi et al. (7)).
- The open source model for Rheumatoid Arthritis. See Incerti et al. (9) and https://github.com/InnovationValueInitiative/IVI-RA
- A number of models for Chronic Obstructive Pulmonary Disease. See Hoogendoorn et al. (10). A recent additional model is the open source EPIC COPD model by Sadatsafavi et al. (11) See https://www.dynamo-hia.eu/
- One of the earliest examples of a disease specific model is the CHD model from Weinstein et al. (12)

Questions regarding terminology and definitions

1.   Do you agree to our definition of a disease specific model as:

"A simulation model that covers a sufficient length of disease trajectory to accommodate the evaluation of a range of health care technologies. Its patient population represents setting specific epidemiology to enable projections of policy scenarios. This enables its repeated use for the health economic evaluation of new and existing health care technologies and to support evidence based health care policy regarding a certain condition."

If not, please provide an alternative definition.

My definition would be:

2.   What elements that may define a disease model do you consider essential? (please indicate all elements you consider essential)

1. Suitable to evaluate a wide range of interventions
2. Conceptual model acceptable to all stakeholders
2. Models the entire disease trajectory from healthy to death
3. Covers all patients
4. Includes information on demography and epidemiology, i.e. total prevalence and incidence in a jurisdiction
5. Suitable/intended for repeated use in health economic evaluations
6. Suitable/intended for supporting health care policy making by providing projections of policy scenarios, like the number of future patients in case of unaltered health care.
7. Suitable to consistently evaluate and compare decisions at different disease stages (e.g. prevention, diagnosis, primary treatment, palliative care)
8. Suitable to model different consecutive treatments, like first and second line cancer treatments.
9. Comprising connections between decisions at different disease stages (e.g. different choices regarding palliative care affect evaluation of diagnosis modes)

Essential elements are numbers : (best would be a few)

Further essential elements not listed are:

2.   Possible application areas of disease specific models
Disease specific models apply for health economic evaluations of certain interventions, but as indicated in the literature also lend themselves to other applications.

Outcomes of the model hence should be an option of choice to the model user. They should not be confined to costs per QALY gained for one intervention compared to another.

Other outcomes could be: Total number of patients in certain disease stages over time; total costs generated by the model population over a certain time horizon, possibly in certain subcategories, like disease severity, age, gender; total QALYs generated by the model population over a certain time horizon. Numbers of events;
Examples of applications using these outcomes are:

- Resource allocation: Optimization of resources over a set of interrelated interventions over the entire disease pathway of interest.
- Budget impact estimation: estimation of the overall costs (and health benefits) of certain policy choices for a jurisdiction, within a certain year/range of years.
- Guideline development: support evidence over the costs and benefits of several interventions in a consistent way.
- Epidemiological projections: provide insight in the expected numbers of patients in certain disease stages over time, based on currently observed numbers and trends, possible for a set of alternative scenarios.
- Policy evaluation: Compare alternative policies concerning prevention and treatment.

Question concerning application of disease specific models

Please discuss whether you agree to the above mentioned possibilities or foresee any problems, and indicate any other use of disease models which you are aware of.

The following applications are relevant to disease specific models:

3.   Organizational and methodological issues concerning the use of disease specific models

Several issues arise related to the development and use of disease specific models. These can be related to methods (how to properly build a disease specific model), to organizational issues (how to finance maintenance of a disease specific model), or to both. We have listed a few examples, without a claim for completeness. We would welcome your comments and additions. Of course some issues will only be relevant for specific applications.

Issues for use of disease specific models are:

Mostly organizational
- Funding for development, that is resources and time needed to build disease specific models
- Funding for maintenance of disease specific models
- Funding for hosting / Q&A to support users of disease specific models
- How to ensure sufficient transparency of model structure, assumptions and input data.
- How to ensure access to models for potential users.
- Ownership (model and results)
- Identification and role of stakeholders
- Mandatory or optional use in policy contexts

Mostly methodological
- Minimal requirements regarding validation status and uncertainty analysis
- Required model depth/degree of detail /range of outcomes
- Way of updating evidence that does not require adjustment of model structure (user interface)
- Way of updating evidence that would require adjustment of model structure
- Freedom to users to adjust the model to their own requirements
- Transferability (what part of a model is to be based on setting specific data?)
- Limits to acceptable run-time
- Possibility to split models into model components (modules), e.g. risk engine, costing module.
- How to improve model understanding (face validity, explanation)

Question concerning organizational and methodological issues

Please indicate any other issues you can think of and explain why they require attention when using disease specific models in support of health economic decision making or health policy making in general.

Issues relevant for use of disease specific models

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Questionnaire Round 2
Disease specific models for health care policy in the Netherlands
General introduction to the project (can be skipped when you are
familiar with the project and/or participated in round 1)

The Dutch National Healthcare Institute has initiated the current project,
to investigate disease models as a possible option to support more
structured use of health economic evaluation and other applications of
disease models as part of its policy advisory role. Currently health
economic evaluations and other simulation model outcomes play a role
in reimbursement decisions concerning drugs with added value, but less
so in reimbursement decisions on non-drug treatments, in guideline
development, or in the program "Zinnige zorg" (which critically
evaluates all healthcare within a certain area of care, e.g. respiratory
disorders, or mental health) .

The research team working with the Dutch Healthcare Institute on this
project consists of the following researchers and institutions:
- Dutch National Institute for Public Health and the Environment
  (RIVM): Dr TL Feenstra, Dr GA De Wit; Dr A van Giessen.
- University Medical Centre Utrecht: Dr GA de Wit; Dr GJW
  Frederix; Dr J Wang.
- University of Twente: Dr H Koffijberg;
- Maastricht University Medical Centre: Prof Dr M Joore; Dr B
  Ramaekers; MSc X Pouwels
- Groningen University: Prof Dr TL Feenstra

In addition, Prof Dr Paul Tappenden (Professor of Health Economic
Modelling, HEDS, ScHARR, University of Sheffield, Sheffield, UK) and Dr
Hossein Afzali (Senior Lecturer, Adelaide Health and Medical Sciences ,
The university of Adelaide, Australia) are involved as project advisors.

The project will consist of three tasks:
1. Build and provide access to an actual disease model, by way of a
   model interface.
2. Investigate the methodological and structural issues involved in
   using disease models for health care policy support
3. Report on the findings

As part of task 2, we have involved a panel of international experts, the
current document is the second round of expert involvement. We re-
approach the original panel and additionally consult new experts and
stakeholders that were less well represented in our panel.

Based on our first round we have:
- Gathered and processed 51 responses from the panel (see
  attached summary)
- Presented results to ZIN-representatives in a meeting
- Presented and discussed first findings with two separate groups
  of health economic decision modelers (At HERC in Oxford UK and
  at the MountHood Diabetes Asia Meeting in Seoul, South-Korea).
- Added remarks from these three presentations to the summary
  of findings.

- Discussed panel responses in a team meeting, focusing on items 3 and 4. In this meeting we decided on inclusion of items/formulation and on the way to present results to the panel.
- Based on the summary document produced a new questionnaire, which is the current document.

Disease modelling in support of priority setting in healthcare, round 2

This document consists of 7 pages of text, with 5 questions you are kindly asked to answer. Please feel free to add any comments you consider necessary to explain your points. Many thanks for your cooperation.

This document very briefly summarizes findings from the first round of expert panel consultation, and asks for feedback. The results of round 1 are more elaborately summarized in a companion document, for your information. The type of consultation differs by topic. For topics 1 and 2, we ask for your final comments, that is, you can either agree, or disagree, but we do not elicit subtle changes. Of course, comments are always welcome. For topics 3 and 4, we have tried to condense from the large amount of insights raised by the panel and ask for item-wise scoring and comments.

Topic 1: Terminology and definition.
In the round 1 panel document we provided the following definition of a "disease specific model":
"A simulation model that covers a sufficient length of disease trajectory to accommodate the evaluation of a range of health care technologies. Its patient population represents setting specific epidemiology to enable projections of policy scenarios. This enables its repeated use for the health economic evaluation of new and existing health care technologies and to support evidence based health care policy regarding a certain condition."

We asked for comments on this definition. Also we discussed terminology, starting with "disease specific model" as the term used in the panel document.

Summary of response regarding terminology
Table 1 below summarize the general findings in a quantitative sense. Please note that our sample consisted of preselected participants and was not balanced, for example, with respect to age, gender or experience. We started with the active participants of the AdViSHE panel and added participants with modelling knowledge from our network. The aim was saturation (qualitative research), not a representative survey. This implies that these numbers should be interpreted with care.

During the presentations, the audience indicated that the terms disease model and disease specific model are quite general, while the term generic disease model is confusing, since it seems to indicate a multiple diseases model. The same will hold for comprehensive disease model.

Table 1 Summary panel responses regarding terminology

Agree to terminology	1		
Implicitly agree[3]	41		
Not agree	7	provided alternative	7
NA	2	provided alternative	1
Total answers	51		8

Alternative terms

The 9 alternatives (7 from the panel + 2 more from presentations) provided for "disease specific model" were:
- Generic disease model. General disease model.
- Policy Model for reuse
- Disease model (vs stage or setting specific model).
- Non-single-use model
- Whole disease model
- Include "policy" in the name
- Comprehensive disease model
- Reference model
- Multiple use model

QUESTION: 1)

The new term suggested by team: Multi-use disease model

Argumentation: Disease model, Disease specific model and generic disease model were considered too vague or confusing. Repeated use/multiple use/for reuse/no single use was indicated by many participants as a relevant and distinctive feature. Policy model was also repeatedly suggested, but is according to the team not very distinctive.

Question: Given information on alternative terms, please indicate your agreement/disagreement to this term: AGREE/DISAGREE

Summary of response regarding definition.
Table 2 below summarize the general findings in a quantitative sense. Please note that our sample consisted of preselected participants and was not balanced, for example, with respect to age, gender or experience. We started with the active participants of the AdViSHE panel and added participants with modelling knowledge from our network. The aim was saturation (qualitative research), not a representative survey. This implies that these numbers should be interpreted with care.

Quite some respondents proposed an alternative definition. Most alternative definitions were minor alterations to our general definition. Most comments/alterations concerned the wording of health care technologies (often considered as too narrow), the use of the term epidemiology, since this also refers to a field of research, and the

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[3] That is, the participant used the term "disease specific model" and did not comment on it.

"sufficient" length of the disease trajectory, which was considered vague, with some attempts to specify this.

Several respondents also stressed the need to accommodate treatment sequences. In total 5 respondents opposed the whole idea of reference models, with statements stressing the need of specific models for specific applications, 4 of these also explicitly disagreed to the definition.

Remarks were also made concerning comorbidities, with mixed views on whether or not the model should cater for multiple diseases.

Part of the respondents supports the idea to reflect full disease prevalence and incidence, and to account for subgroups and trends in time. Another part of the respondents favors a deliberate choice where to start in the disease trajectory.

In short the findings were: (1) add notion about flexible adaptation; (2) be careful about the use of term health care technologies but rather use the more generic term interventions; (3) Be careful with the term epidemiology but rather stress that it is about setting specific disease prevalence, incidence, and (4) Use health policy rather than policy.

Table 2 Summary regarding definition

agree to definition	19		
suggested small changes in wording	24	provided an alternative	18
not agree	4	provided an alternative	1
NA	4		
Total answers	51		19

Topic 2: Elements considered essential to characterize a multi-use disease model

The panel survey listed 10 different elements that may define a disease specific model and asked respondents to rank them for importance. The panel was asked to list at least 5 important elements and add any elements not mentioned in the list that they deem also of importance. The number of total respondents indicating each item to be important or less important or not mentioning anything about it is presented in figure 1 below. In total 5 respondents did not answer this question, represented by the grey bars.
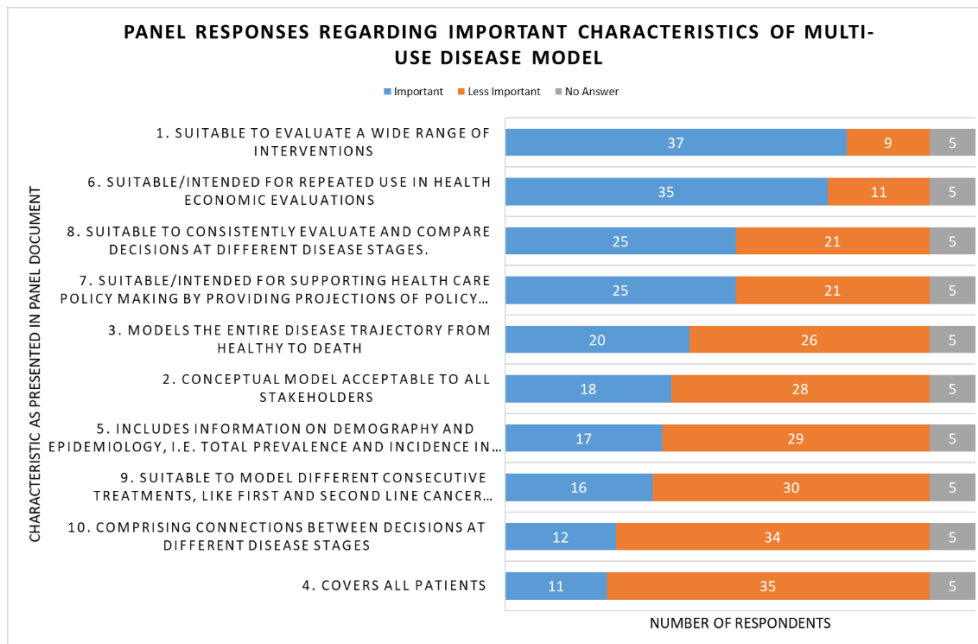
Figure 1 Overview of panel responses

This graph shows that two elements are considered important by many respondents, namely "suitable to evaluate a wide range of interventions" and "suitable for repeated use". Two further elements were considered important by more than half of those who answered to this question, being "suitable to consistently evaluate and compare decisions at different disease stages" and "suitable for supporting health care policy making by providing projections of policy".

Based on these results, this supports the inclusion of "multi-use", projections and a wide range of interventions in our definition and terminology. Consistency over disease stages was however not covered by our definition. We added this, and also accounted for comments from topic 1.

QUESTION 2: Please consider the following new definition:

A Multi-use disease model is "A health economics decision model that properly represents the length and dynamics of a disease trajectory to accommodate the evaluation of a range of current and future health care interventions. It enables projections of policy scenarios, based on setting specific epidemiological parameters. When several disease stages are included, consistent comparisons over these stages are possible. This enables its repeated use, possibly after adaptations, for health economic evaluations and to support evidence based health care policy regarding a certain condition."

Please indicate whether your agree or not with this new definition: AGREE/DISAGREE (provide reason if possible)

Topic 3: Applications for multi-use disease models

The panel received a list of possible applications for multi-use disease models, mostly based on previously published applications (see summary document). Then we asked the panel to comment on these and add any other applications they missed in our list.

In a next step, the team selected applications that could be considered relevant to a public authority with the aim to advise the Ministry of Health concerning coverage/reimbursement, clinical guidelines and horizon scans (like ZIN). This second step was intended to keep the scope of applications manageable and consistent with the project scope.

Comments to the listed applications concerned the terminology of "epidemiological projections". It was suggested to use the term projections instead (given the abovementioned issues with the term epidemiology). Also at least two respondents considered such projections to be beyond the scope of multi-use disease models and/or to require more data. Respondents also criticized the use of multi-use disease models for clinical guidelines and for resource allocation: "In my opinion, the clinical guidelines should always be written irrespective of any economic elements, and be fully based on clinical effectiveness." "Resource allocation needs a different model than CEA." Concerning resource allocation, other respondents noted that models for resource allocation would need to cover multiple diseases. We learned from the latter that the application of resource allocation should be limited to allocation within a disease, or even within a certain part of a disease trajectory.

QUESTION 3:

To further specify suitable applications, we ask you to select a maximum of 5 important applications from Table 4 below and rank them in order of importance. With a government agency like NICE, HAS, IQWIG, or the Dutch Healthcare authority in mind.

Table 3 Applications for multi-use disease models

Application (similar applications were combined)	Priority score (please give a score 1,2,3,4,5, or 0 with 5 indicating highest priority. Please use each score only once)
Resource allocation: Optimization of resources over a set of interrelated interventions over the entire disease pathway of interest.	
Budget impact estimation: estimation of the overall costs (and health benefits) of certain policy choices for a jurisdiction, within a certain year/range of years.	
Guideline development: support evidence over the costs and benefits of several interventions in a consistent way	
Projections: provide insight in the expected numbers of patients over time.	
Compare alternative policies concerning prevention and treatment	
Exploration: new treatment options/scenario analysis/subgroups (e.g. by SES)/biological mechanisms	
Support government investment decisions	
Identification of key uncertainties and their potential impact	
Equity analyses: You may want to study the effect of different interventions in people with e.g. various economic status	
Umbrella trials (network meta-analysis type of use)	

Please add your scores to the table above. Any comments can be listed below

Topic 4: List of issues multi-use disease models

In the fourth topic of the panel document, respondents were asked to list and discuss issues expected when implementing and using a multi-use disease specific models for support of healthcare policy making. A short list of potential issues was provided and comments and additional issues were solicited.

All responses were coded by two researchers independently, who then drafted a list of issues which was again double checked and discussed, first by the two researchers and then in a consensus meeting by the team. This led to a condensed draft gross list of potential issues, sorted into categories, based on similarity of topics, and split into recommendations and issues (see summary document). The team has further reduced the number of items in the table by removing/combining recommendations and items that have a substantial overlap and/or feel very clearly outside the setting of our research aim. (To support the Dutch Healthcare institute concerning the use of disease specific models for policy support)

To further prioritize these issues, in this second round in we ask you to score items in the new table for relevance and feasibility, given the perspective of a public authority (e.g. the Dutch Healthcare Institute) and to score the recommendations for acceptability. To reduce the workload for each panel member, we have distributed the items over the panel members, so each panel member has to score at most 8 issues and 5 recommendations. The complete table is printed at the end of this document.

Relevance scores concern the question whether it is a prerequisite to solve this issue for successful implementation of multi-use disease models in health policy decision making. With feasibility we mean your assessment of the challenges involved in solving this issue. With acceptability we mean that the solution is in your opinion scientifically sound (when applicable) and is workable for a governmental agency.

QUESTION 4A:

Please score the issues listed below on relevance (highly relevant, moderately important, not important) and feasibility. (not possible, ambitious, certainly doable)

Any comments or new issues you would like to add? (please see complete table -page 11)

Table 4 Issues concerning the application of multi-use disease models to score for relevance and feasibility:

Category	Issue/challenge/choice to be made	SCORE FOR RELEVANCE	SCORE FOR FEASIBILITY
Organization (access & ownership) **Money, legal, IP, etc.**	Funding for maintenance		
	Mandatory or optional use in policy contexts		
	Licensing + how to organize this		
Development of model	Model complexity/depth/degree of detail (balance specificity and generality)		
Input data	When model is used repeatedly, and is based on patient level data, how is model use compatible with GPRD.		
Validation and transparency			
Model use	Transferability (what part of a model is to be based on setting specific data?)		
Model results	How to improve model understanding (face validity, explanation)		
Model maintenance (technical)	Time required to get approval for adaptations of the model		

QUESTION 4B:

Please score the solutions/recommendations listed below on acceptability (highly desirable, acceptable, unacceptable). Feel free to add new suggestions and indicate tensions.

Table 5 Recommendations for application of multi-use disease models to score for acceptability

Category	Recommendation	SCORE FOR ACCEPTABILITY
Organization (access & ownership) **Money, legal, IP, etc.**	Ensure future access by having models maintained by a public authority.	
Development of model	Ensure interdependencies between decisions at different stages of a disease	
Input data	Has to represent trends over time	
Validation and transparency		
Model use		
Model results	Ensure proper storage of results. For archiving of research results.	
Model maintenance (technical)	Have regular updates + version control	

Comments:

Table 6 Complete table of issues

Category	Issue/challenge/choice to be made	RELEVANCE	BILIYT
Organization (access & ownership) Money, legal, IP, etc.	1. Funding for maintenance 2. Funding for hosting / Q&A to support users of disease specific models 3. Ownership (model and results) 4. Role of stakeholders 5. Mandatory or optional use in policy contexts 6. What kind of software is allowed or suitable (in relationship to accessibility/users/regulation) 7. Liability agreement for wrong results (caused by wrong model) 8. Prevent misuse (uniformed, inappropriate), 9. Licensing + how to organize this 10. How to ensure collaboration (synergy) between different research groups/ stakeholders 11. Confidentiality agreement (e.g. a company using it on a drug in development)		
Development of model	12. Consider a modular approach 13. Model complexity/depth/degree of detail (balance specificity and generality) 14. Should a multi-use model be an empty shell or a setting specific model 15. Funding for development 16. How to ensure sufficient transparency of model structure, assumptions and input data.		
Input data	17. To find an acceptable solution to the tension transparency & replicability versus privacy patient level data 18. When model is used repeatedly, and is based on patient level data, how is model use compatible with GPRD.		
Validation and transparency	19. Communicating model limitations 20. Risk in using one model structure; blinder for structural uncertainty; 21. Comparability with other models or model outcomes		
Model use	22. Transferability (what part of a model is to be based on setting specific data?) 23. How to ensure access to models for potential users. 24. Limits to acceptable run-time		
Model results	25. Organize governance for access to model results of certain applications. 26. How to improve model understanding (face validity, explanation)		
Model maintenance (technical)	27. Should there be an 'official' (updated) version. 28. How to have a sustainable knowledge base (expertise sits in humans) on the model including transparent documentation 29. Ensure sufficient adaptability		

Category	Issue/challenge/choice to be made	RELEVANCE	BILIYT
	30. Time required to get approval for adaptations of the model		
	31. Way of updating evidence that does not require adjustment of model structure (user interface)		
	32. Way of updating evidence that would require adjustment of model structure		

Table 7 Complete table of recommendations

Category	Recommendation	SCORE FOR ACCEPTABILITY
Organization (access & ownership) Money, legal, IP, etc.	1. Ensure future access by having models maintained by a public authority. 2. Ensure independent owner, e.g. a public authority (independent of academic centers) 3. Have free access 4. Have licensed access 5. Have a registry of models - to help identifying models	
Development of model	6. Accommodate for regular updates (e.g. based on automated links to registries/claims data) 7. Ensure interdependencies between decisions at different stages of a disease 8. Make a deliberate choice were to start, e.g at the healthy population or not. 9. Do include the healthy population 10. Do not include the healthy population 11. Include subgroups/heterogeneity	
Input data	12. Should be Transparent. (FAIR) 13. Has to represent trends over time	
Validation and transparency	14. Use very strong validation requirements 15. Perform revalidation after updates	
Model use	16. Ensure an accessible interface 17. Ensure freedom to users to adjust the model to their own requirements and/or data 18. A model should only be used by the developers	
Model results	19. Ensure proper storage of results. For archiving of research results.	
	20.	
Model maintenance (technical)	21. Have regular updates + version control	

End of document. Thank you for your efforts to fill out the questions!

Summary Report Round 1
Summary findings expert panel round 1
The current document summarizes the findings from the first round of expert panel consultation. It is meant as a feedback for those of you that participated in this round. Also it is meant as informative for new participants. It also contains a brief description of the background of the project (page 9). It goes along with a brief document that for each topic asks your opinion or agreement and contains the results in a more condensed way.

Topic 1: Terminology and definition.

In the panel document we provided the following definition of a "disease specific model" as follows:

"A simulation model that covers a sufficient length of disease trajectory to accommodate the evaluation of a range of health care technologies. Its patient population represents setting specific epidemiology to enable projections of policy scenarios. This enables its repeated use for the health economic evaluation of new and existing health care technologies and to support evidence based health care policy regarding a certain condition."

which we asked you to comment upon. Also we discussed the proper term, starting with disease specific model as the term used in the panel document.

Overall summary of responses
Tables 1 and 2 below summarizes the general findings regarding the definition, in a quantitative sense. Please note that our sample consisted of preselected participants and was not balanced, for example, with respect to age, gender or experience. We started with the active participants of the AdViSHE panel and added participants with modelling knowledge from our network. The aim was saturation (qualitative research), not a representative survey. This implies that these numbers should be interpreted with care and in connection with the summary of qualitative findings below.

Table 4 Summary regarding definition

agree to definition	**19**		
minor changes	24	provided an alternative	18
not agree	4	provided an alternative	1
NA	4		
Total answers	51		19

Table 5 Summary regarding terminology

Agree to terminology	**1**		
Implicitly agree[4]	41		
Not agree	7	provided alternative	7
NA	2	provided alternative	1
Total answers	51		8

In total 9 (7 as in table 2 and 2 suggested in presentations) suggestions for new terminologies for "disease specific model" were given:
1. Generic disease model. General disease models.
2. Policy Model for reuse
3. Disease model (vs stage or setting specific model).
4. non-single-use model
5. Whole disease model
6. Include "policy" in the name
7. Comprehensive disease model
8. Reference model
9. Multiple use model

During the presentations, the audience indicated that the terms disease model and disease specific model are quite general, while the term generic disease model is confusing, since it seems to indicate a multiple diseases model. The same will hold for comprehensive disease model.

The team suggests the panel in this second round to opt for "multi-use disease model".

Summary of comments regarding definition.
Most alternative definitions were minor alterations to our general definition. Most comments/alterations concerned the wording of health care technologies (often considered as too narrow), the use of the term epidemiology, since this also refers to a field of research, and the "sufficient" length of the disease trajectory, which was considered vague, with some attempts to specify this.

Several respondents also stressed the need to accommodate treatment sequences.

Around 5 respondents opposed the whole idea of reference models, with statements stressing the need of specific models for specific applications.

Remarks were also made concerning comorbidities, with mixed views on whether or not the model should cater for multiple diseases. Given our research aim, we deliberately choose not to cover multiple disease models. Some of our examples in the panel document were, which may have caused some confusion.

Part of the respondents supports to reflect full disease prevalence and incidence, and to account for subgroups and trends in time. Another part

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[4] That is, the participant used the term "disease specific model" and did not comment on it.

of the respondents favors a deliberate choice where to start in the disease trajectory. We prefer the latter, for reasons of feasibility and in line with our task/study aims.

For the 18 rephrased definitions, Table 3 below provides insight into what was changed/considered irrelevant (NA). One rephrase seemed not to be different from the original definition. Table 3 concentrates on alternatives provided for different elements in the definition. In short the findings were: (1) add notion about flexible adaptation; (2) be careful about the use of term health care technologies but rather use the more generic term interventions?; (3) Be careful with the term epidemiology but rather stress that it is about setting specific epidemiology, and (4) Use health policy rather than policy.

In addition to these alternative formulations, comments made in Topic 2 also have implications for the definition, see below.

Table 6 Elements in alternative definitions provided

simulation model	sufficient length of disease trajectory	range of hc technologies	represents setting specific epidemiology	projections of policy scenarios	repeated use	health econ eval	new and existing	support evidence based hc policy	a certain condition
any model	of a patient's disease trajectory	to simulate the evolution of the disease.	setting specific epidemiology and demography	projections of health policy scenarios.	based on repeatedly adapt such model	to support scenario analysis			a specific disease
a stochastic model	a simplified representation of the disease	a range of current and future health care technologies	incorporates epidemiology	algorithms to enable projections				support evidence based health care policy , as well as budget impact analysis"	for this disease in relation to all diseases
a decision analytic model	represents properly the length and progress of the disease trajectory	Its population characteristics	to configure the model to the baseline risks of specific patient populations defined in terms of demographic and clinical characteristics.	results in different scenarios				in order to set evidence-based priorities for policy	allows "easy" adaptation to new developments , and easy adaptation to specific settings
a mathematical framework	covers (full) disease trajectories	a range of health care technologies.	that has been validated against observational data						

| simulation model	sufficient length of disease trajectory	range of hc technologies	represents setting specific epidemiology	projections of policy scenarios	repeated use	health econ eval	new and existing	support evidence based hc policy	a certain condition
a dynamic simulation model	incorporates all relevant knowledge about the course(s) a disease may take	of what is expected to happen with changes in how the disease is managed.	suitable and sufficient epidemiological evidence						
	the manifestations of the disease	any health care technologies.	represent setting specific epidemiological parameter						
	covers lifetime disease trajectory	a range of current and future health care technologies.	The evidence used to inform it represents setting specific epidemiology						
	covers the whole length of disease trajectory	a wide range of health technologies(or health programs).	Its patient multicohort population represents setting specific epidemiology						
			Its population analysis represents setting specific epidemiology						

Topic 2: Elements considered essential to characterize a multi-use disease model

In our survey, we listed 10 different elements that may define a disease specific model and asked respondents to identify those elements that they considered most important. The panel was asked to list at least 5 important elements and add any elements not mentioned in the list that they deem also of importance.

The following 10 elements were listed
1. Suitable to evaluate a wide range of interventions
2. Conceptual model acceptable to all stakeholders
3. Models the entire disease trajectory from healthy to death
4. Covers all patients
5. Includes information on demography and epidemiology, i.e. total prevalence and incidence in a jurisdiction
6. Suitable/intended for repeated use in health economic evaluations
7. Suitable/intended for supporting health care policy making by providing projections of policy scenarios, like the number of future patients in case of unaltered health care.
8. Suitable to consistently evaluate and compare decisions at different disease stages (e.g. prevention, diagnosis, primary treatment, palliative care)
9. Suitable to model different consecutive treatments, like first and second line cancer treatments.
10. Comprising connections between decisions at different disease stages (e.g. different choices regarding palliative care affect evaluation of diagnosis modes)

Based on answers from 51 respondents, the percentage indicating each item to be important or less important or not mentioning anything about it was scored. In total 5 respondents did not answer this question, so the grey bars represent this. The elements were sorted by the number of respondents that considered this item to be important.
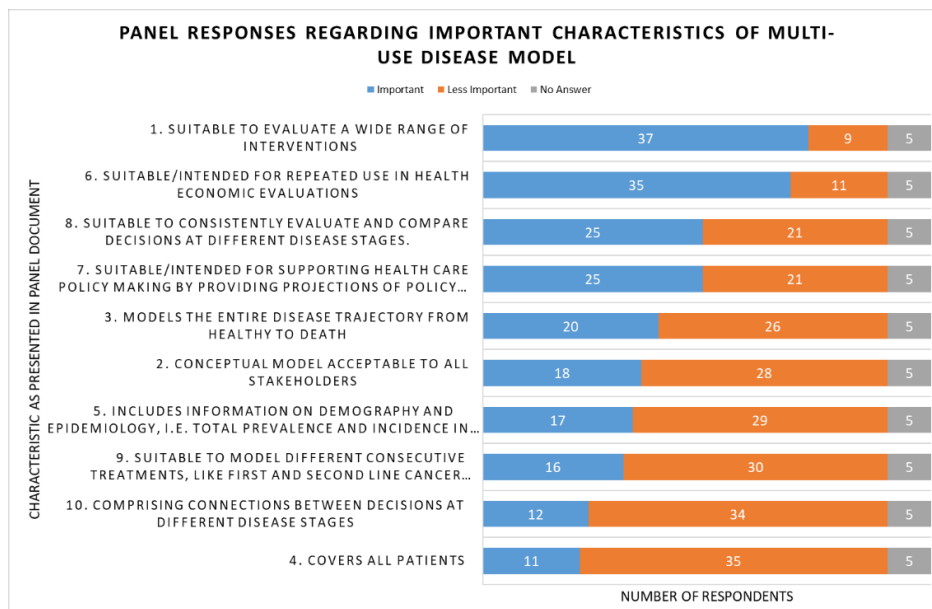
Looking at this graph, two elements are considered important by many respondents, namely covering a range of interventions and being suitable for repeated use. Two further elements were considered important by more than half of those who answered to this question, being option to produce policy projections and being consistent over disease stages.

Based on these results, this supports the use of "multi-use", projections and wide range of interventions in our definition and terminology. Consistency over disease stages is not currently covered by our definition. We added a sentence for this:

A Multi-use disease model is "A health economics decision model that properly represents the length and dynamics of a disease trajectory to accommodate the evaluation of a range of current and future health care interventions. It enables projections of policy scenarios, based on setting specific epidemiological parameters. When several disease stages are included, consistent comparisons over these stages are possible. This enables its repeated use, possibly after adaptations, for health economic evaluations and to support evidence based health care policy regarding a certain condition."

Topic 3: Applications for multi-use disease models

We provided the panel with a list of possible applications for multi-use disease models (see Table 7. below), mostly based on previously published applications. Then we asked the panel to comment on these and provide any other applications they missed in our list. These comments are summarized in table 5 below.

In Table 4, we have added a column in which we indicate whether the proposed application could be considered relevant to a public authority with the aim to advise the Ministry of Health concerning coverage/reimbursement, clinical guidelines and horizon scans.(like ZIN) This second step was performed by the team and intended to keep the scope of intended applications manageable.

Comments to the listed applications are listed in table 5 below. They concerned the terminology of "epidemiological projections". It was suggested to use the term projections instead. Also at least two respondents considered such projections to be beyond the scope of multi-use disease models and/or to require more data.

Respondents also criticized the use for clinical guidelines and for resource allocation: "In my opinion, the clinical guidelines should always be written irrespective of any economic elements, and be fully based on clinical effectiveness." "Resource allocation needs a different model than CEA." Concerning resource allocation, other respondents noted that models for resource allocation would need to cover multiple diseases. We learned from the latter that the application of resource allocation should be limited to allocation within a disease, or even within a certain part of a disease trajectory.

Table 4 below lists our applications followed by the new applications mention by the panel, as well as whether or not these would be relevant for our current purpose (team's opinion). Applications that the team considered as already covered or not feasible (even with a huge amount of time to build the model) were removed from the list of new applications.

Table 7 Applications for multi-use disease models

Application (similar applications were combined)	Relevant for purpose of ZIN
Resource allocation: Optimization of resources over a set of interrelated interventions over the entire disease pathway of interest.	Possibly
Budget impact estimation: estimation of the overall costs (and health benefits) of certain policy choices for a jurisdiction, within a certain year/range of years.	Yes
Guideline development: support evidence over the costs and benefits of several interventions in a consistent way	Possibly
Projections: provide insight in the expected numbers of patients over time.	Possibly
Compare alternative policies concerning prevention and treatment	Yes
Educational or training purposes	NO
Exploration: new treatment options/scenario analysis/subgroups (e.g. by SES)/biological mechanisms	Possibly
Support decisions by insurance companies	NO
Support government investment decisions	Possibly
Assist in trial design and research prioritization.	NO
Identification of key uncertainties and their potential impact	Possibly
Foresee (future resource use and) capacity limitations	NO
Drug/device development decisions and R&D for industry, for (innovative and expensive) drugs	NO
Individual prognosis	NO
Equity analyses: You may want to study the effect of different interventions in people with e.g. various economic status	Possibly
Clinical trial simulation, synthetic control arms	NO
Umbrella trials (network meta-analysis type of use)	Possibly

Table 8 Overview of comments to list of applications

Issues with the term epidemiological projections (disease risk prediction as better alternative)	**1**
For resource allocation/budget impact estimation not only estimation of outcomes of interventions/policy choices for one disease are necessary, but also for other diseases (and interventions) are necessary.	2
Model complexity (and overfitting)	3
Time to market is ever decreasing which leads to things like companies getting reimbursement for cancer drugs with only phase-2 OS data). I am unsure if the world is ready yet.	1
Ensure validation and use by wide range of audience/users/stakeholders	1
Problems with comparability with other models or model outcomes	1
Issues with epidemiological projections (beyond the scope of this model)	2
A wide range of outcomes should be generated: **- disease-specific QoL measures, because decision problems may be limited to the disease-domain** **- include efficacy outcomes other than QALYs for those jurisdictions where these are not used** **- many types of intermediate outcomes for different stakeholders/audience**	3
Problems with lack of data and amount of assumptions involved.	1
Guideline development: "In my opinion, the clinical guidelines should always be written irrespective of any economic elements, and be fully based on clinical effectiveness."	1
Epidemiological projections: Good quality real-time RWE databases should be available to come up with these numbers. Currently, getting good quality epi data can be challenging and lagging behind.	1
Not necessary to have many/all applications in 1 model	2
Problems with choosing the right modelling approach wrt aim. Resource allocation needs different model than CEA.	2
Evidence of effectiveness that can be used is often limited. Cancer, where treatment lines and combinations are studied, is a notable exception.	2

Topic 4: List of issues multi-use disease models

In the fourth topic of the panel document, respondents were asked to list and discuss issues expected when implementing and using disease specific models for support of healthcare policy making. A list of potential issues was provided and comments and additional issues were solicited.

All responses were coded by two researchers independently, who then drafted a list of issues which was again double checked and discussed.

This led to a draft gross list of potential issues, sorted into categories, based on similarity of topics. This list was then resorted and condensed during a consensus meeting by the research team. The team removed items that could be considered a general issue in HE decision modelling, or recommendations that would hold for all HE decision models. We tried to err on the conservative side. The result is presented in table xx below. This contains new issues raised by the panel, as well as issues already listed in the panel document. The table presents recommendations as expressed by the panel members as well as issues perceived by them. In a new table, the team has reduced the number of items in the table by skipping recommendations and items that we consider to be irrelevant within the setting of our research aim. (To support the Dutch Healthcare institute concerning the use of disease specific models for policy support) Recommendations strongly varied in degree of concreteness, and issues in level of detail. When possible we combined them.

Table 9 Selected issues and recommendations

Category	Recommendation	Issue/challenge/choice to be made
Organization (access & ownership) Money, legal, IP, etc.	• Ensure future access by having models maintained by a public authority. • Ensure independent owner, e.g. public authority (independent of academic centers) • Have free access/have licensed access • Have a registry of models - to help identifying models • Make known how or who to submit models.	• Funding for maintenance ; Funding for hosting / Q&A to support users of disease specific models • Ownership (model and results) • Role of stakeholders • Mandatory or optional use in policy contexts • What kind of software is allowed or suitable (in relationship to accessibility/users/regulation) • Liability for wrong results (caused by wrong model); Prevent misuse (uniformed, inappropriate), • Use of the model to be mandatory or optional • Licensing + how to organize this • (financial) sustainability (=funding for maintenance) • How to ensure collaboration (synergy) between different research groups/ stakeholders • Funding for development, maintenance, hosting, support (Q&A) • Ensure confidential use (e.g. a company using it on a drug in development) • Process: Who can ask for what type of analysis? • Finding models: "Branding", Webpage, … how to set up collaborations and potentially sharing of model/data …
Development of model	• Suitable for PSA at acceptable runtime. (in relation to time of model user) • Accommodate for regular updates (e.g. based on automated links to registries/claims data) • Ensure interdependencies between decisions at different stages of a disease • Not include healthy population/make deliberate choice were to start/Do include healthy population • Include subgroups/heterogeneity	• Consider a modular approach • Model complexity/depth/degree of detail (balance specificity and generality) • Empty shell or setting specific model • Funding • How to ensure sufficient transparency of model structure, assumptions and input data.
Input data	• Should be Transparent. (FAIR) • Include trends over time	• Tension transparency & replicability versus privacy patient level data • When is evidence sufficient to include innovative treatments

Category	Recommendation	Issue/challenge/choice to be made
Validation and transparency	• Use very strong requirements / Validation is important • Perform revalidation after updates • Ensure sufficient transparency of model structure, assumptions and input data.	• Communicating model limitations • Transferability • Risk in using one model structure; blinder for structural uncertainty; • Comparability with other models or model outcomes
Model use	• Ensure an accessible interface • Organize priority users in case of queuing • Ensure freedom to users to adjust the model to their own requirements / data (easy/ user-friendly interface) • Model should only be used by the developers	• Runtime too long for PSA? (solution: metamodel) • Transferability(what part of a model is to be based on setting specific data?) • How to ensure access to models for potential users. • Freedom to users to adjust the model to their own requirements • Limits to acceptable run-time
Model results	• Ensure proper storage of results. For archiving of research results.	• Who has access to model results of certain applications? • Risk in using one model structure; blinder for structural uncertainty; • How to improve model understanding (face validity, explanation)
Model maintenance (technical)	• Have regular updates + version control	• should there be an 'official' (updated) version. • how to have a sustainable knowledge base (expertise sits in humans) on the model including transparent documentation • Balance model complexity and adaptability • Time required to get approval for adaptations of the model • Way of updating evidence that does not require adjustment of model structure (user interface) • Way of updating evidence that would require adjustment of model structure
General requirements		• How acceptable is the entire idea? • Nothing different from single use models • Ensuring acceptance of the model • The benefits are time saving, improved quality analyses, improved comparability. • Not necessary to have many/all applications in 1 model

Remarks that were hard to judge/could not find a place in the table above:
- Compatibility between interface and other models
- Comparison between diseases (if a single model can be designed for different diseases)
- Peer review system only works if people keep checking, using, and improving the models

Criticism/praise on idea mentioned by various panel members, which would not fit in the table:
- one size fits all is not a good idea (horses for courses)/too ambitious (5)
- further adaptation and development will be needed always
- involves unfair wide scope
- it is a very time saving idea

Background information: Perspective of the Dutch Healthcare Institute
ZIN is looking for new ways to better support management of the reimbursement package, including the assessment of medicines. The current assessment system involving individual medicines being assessed against one alternative (instead of assessing several medicines relative to each other) provides insufficient information about the actual value of drugs in clinical practice. In addition, drugs are included in the clinical practice in different combinations and/or in different treatment lines (for example within oncology). The current assessment system offers no possibilities to compare such combinations and sequences.

In addition, actually implemented care has to regularly reviewed concerning effectiveness and cost-effectiveness. Also for this purpose (to re-assess care) ZIN is looking for a tool that can be used for, among other things optimizing decision making.

Multi-use disease models have been extensively described in literature. In recent years, commercial parties have gained experience in developing such models. For example, in the field of diabetes mellitus, within oncology and multiple sclerosis. However, these models are not always used for decision making by Health Technology Assessment (HTA) organizations such as ZIN. An important reason for this is that the current models are not always suitable as a decision tool. This is due to doubts about the quality of the underlying data and because the models are not necessarily made to support decision-making. Furthermore, access can be an issue. Another reason is lack of experience at HTA agencies regarding the design and assessment of multi-use disease models for decision making.

ZIN has various questions about the conditions that multi-use disease models must meet to be suitable for decision making. The current project aims to address these questions. This research into multi-use disease models is hence concerned with the overall question "How can multi-use disease models be used to support package management? "

The following aspects are important here:
— The process of developing a multi-use disease model (for example in collaboration with others parties and academics);
— The issues (both clinical and model technical) that have to be addressed when developing a multi-use disease model and
— An inventory of questions that can be answered with the help of a multi-use disease model.

The panel surveys serve to support answering these questions. Your help is highly appreciated.

Summary Report Round 2
Summary findings expert panel round 2
The current document summarizes the findings from the second round of expert panel consultation. It is meant as a feedback for those of you that participated in this round. It also contains a brief description of the background of the project (page 9).

Topic 1: Terminology and definition.

In the panel document we provided the new term suggested by team: "Multi-use disease model", and asked the panel members to comment upon the revised definition of a "Multi-use disease model" as follows: "A health economics decision model that properly represents the length and dynamics of a disease trajectory to accommodate the evaluation of a range of current and future health care interventions. It enables projections of policy scenarios, based on setting specific epidemiological parameters. When several disease stages are included, consistent comparisons over these stages are possible. This enables its repeated use, possibly after adaptations, for health economic evaluations and to support evidence based health care policy regarding a certain condition."

Overall summary of responses
Figure 1 and 2 below summarize the general findings regarding the tern and definition, in a quantitative sense. Please note that our sample consisted of preselected participants and was not balanced, for example, with respect to age, gender or experience. We started with the active participants of the AdViSHE panel and added participants with modelling knowledge from our network. The aim was saturation (qualitative research), not a representative survey. This implies that these numbers should be interpreted with care and in connection with the summary of qualitative findings below.

New term proposed
With the majority of agreement, the term "multi-use disease model" was approved by the panel. For those who disagreed (7/42, 16.7%), the concerns were mainly focused on the word "Multi-use". "Multi-use" itself might be confusing, since it can refer to several "multi" things, e.g. times, purposes, diseases, treatments, countries. We take this into account by starting any document referring to multi-use disease models with some clear definition.
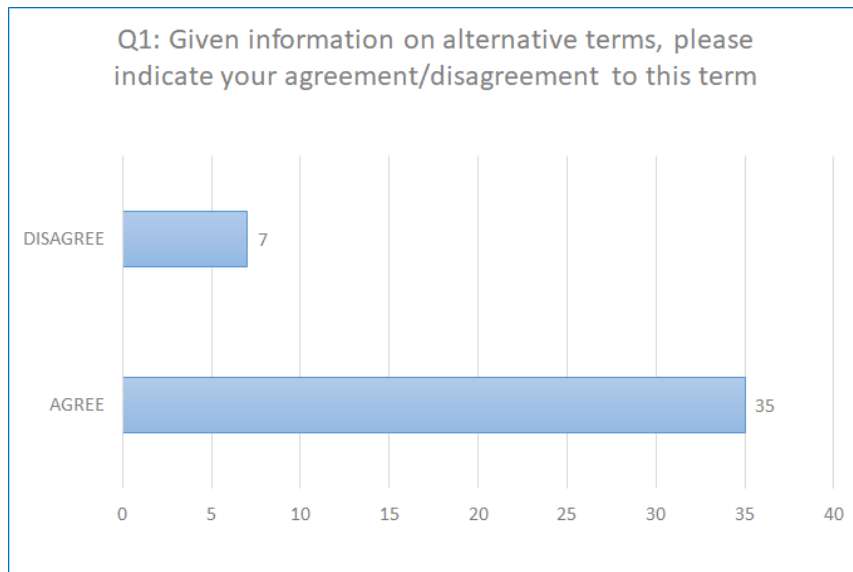
Figure 10 Summary regarding terminology

Revised definition.

The definition as proposed in survey Round 2 was approved by most (33/42, 78.6%) panel members.
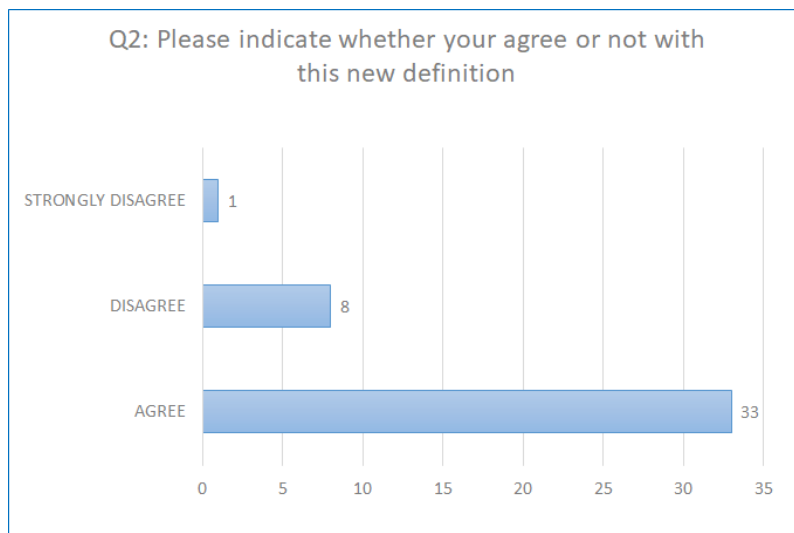

Figure 11 Summary regarding definition

Some remaining comments about the new definition were summarized as follow:
1. Decision model
   "A health economics decision model" seems to suggest that decisions have to be taken based on this mode, however, the multi-use model may also be used for analytical purpose and just provide an advice.
   Given "Health economic decision model" is an existing terminology, and well accepted, we keep it in the definition.
2. Health economics model
   Multi-use models are not necessarily "health economics decision

models", and the health economics aspects are optional and not definitional to these models.

3. The word "properly"
   Several participants commented that the word "properly" is vague and unhelpful. Although it was also used by the AdVISHE team, it is too unfamiliar in this context. They proposed to use "appropriately" or "sufficiently" to replace "properly".

4. Health care interventions
   Health care interventions are too specific. The multi-use models should be suitable for evaluate a wide range of interventions, including prevention which is not about health care. An alternative is suggested to use 'technologies' to replace 'interventions', although this is not a deal breaker.

Topic 2: Applications for multi-use disease models

We provided the panel with a list of selected applications that could be considered relevant to a public authority with the aim to advise the Ministry of Health concerning coverage/reimbursement, clinical guidelines and horizon scans. This second step was intended to keep the scope of applications manageable and consistent with the project scope.

Panel members were asked to select a maximum of 5 important applications from 10 candidate applications and rank them in order of importance (from 1 to 5, with 5 indicating highest priority and 0 for the rest).

Figure 3 presents priority of potential applications based on the answers in the second round. The top two potential applications are comparing alternative policies and resource allocation, which received averaged scores around 2.5. The next three potential applications had averaged scores around 2, which are budget impact estimation, guideline development and identification of key uncertainties and their potential impact. Equity analyses and umbrella trials were considered not very relevant.
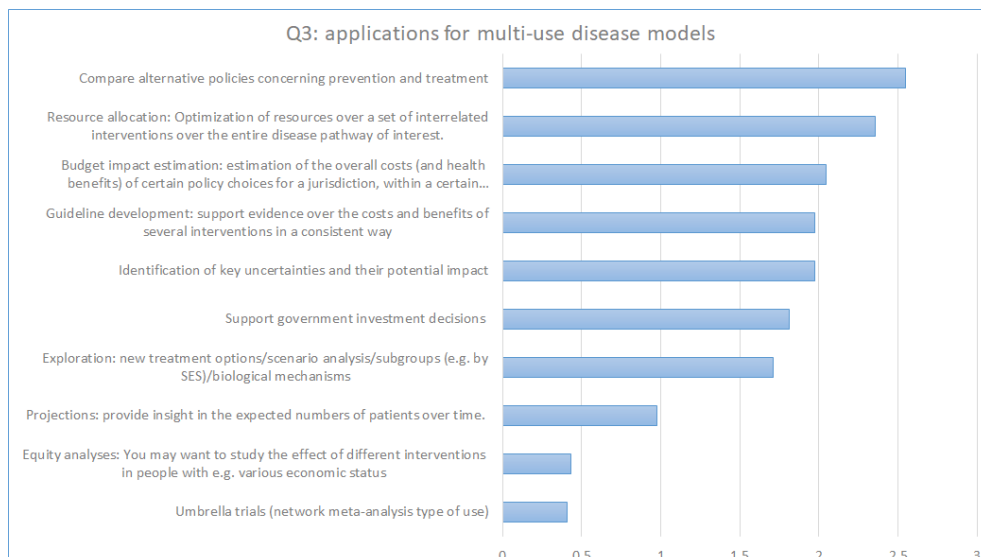

Figure 12 Applications for multi-use disease models

Topic 3: List of issues multi-use disease models

In the third topic of the panel document, a list of issues proposed in a consensus meeting by the team was provided to the panel, and participants were asked to score items in the new table for relevance and feasibility. To reduce the workload for each panel member, one only has to score 7 issues out of 32 issues. 70 points will be distributed to 7 issues, and if the participants would like to score more model issues, their scores will be re-scaled to average 10 points per issue.
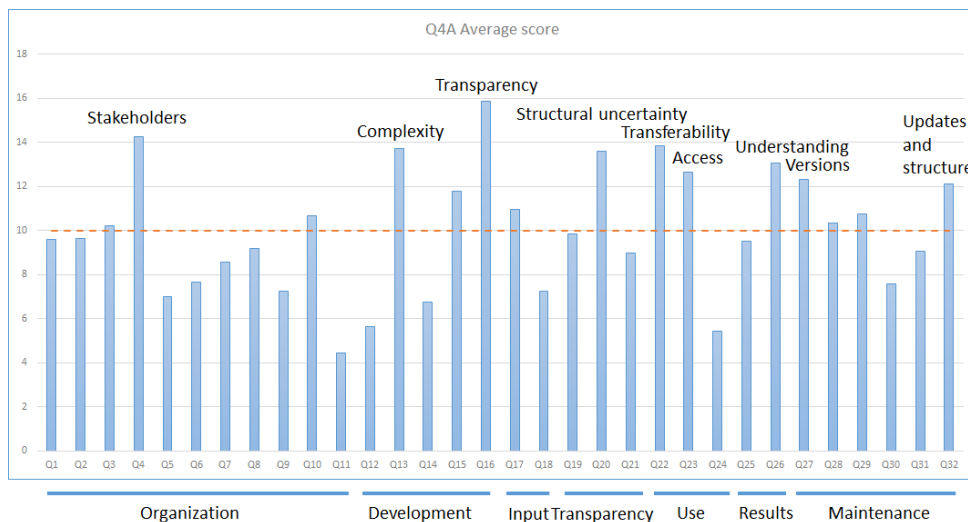

Figure 13 Issues for multi-use disease models

Figure 4 shows the average score of each each issue for multi-use disease models.

Issues received an average points above 12 were considered as important. These issues include:
- Role of stakeholders (Organization (access & ownership))
- Model complexity/depth/degree of detail (balance specificity and generality) (Development of model)
- How to ensure sufficient transparency of model structure, assumptions and input data. (Development of model)
- Risk in using one model structure; blinder for structural uncertainty (Validation and transparency
- Transferability (what part of a model is to be based on setting specific data?) (Model use)
- How to ensure access to models for potential users., more practically (Model use)
- How to improve model understanding (face validity, explanation) (Model results)
- Should there be an 'official' (updated) version. (Model maintenance (technical))
- Way of updating evidence that would require adjustment of model structure. (Model maintenance (technical))

Topic 4: Elements considered as solutions/recommendations to the issues of a multi-use disease model

Following the issues identified in topic 3, a list solutions/recommendations was provided to the panel, and participants were asked to give their opinion on the acceptability (highly desirable, acceptable, unacceptable) of these solutions/recommendations. To reduce the workload for each panel member, one only has to answer 5 questions out of 20.

Scores on recommendations presented in round 2 are summarized in figure 4, clearly the experts would not advise to have a model only be applied by its developers, and to not include the healthy population. The latter is a bit hard to interpret. Licensed access received less support than free access. Large support (≥50% scoring highly desirable) was expressed for regular updates (>80%), proper storage of results, revalidation after updates (>80%), strong validation requirements, including time trends in multi-use disease models, FAIR/transparent modelling, including subgroups& heterogeneity, include the healthy population, accommodate regular updates, free access, and independent model owners.

From this it can be concluded that the expert panel tended towards more extensive models (including healthy population, strong validation requirements, regular updates, FAIR), and public ownership.
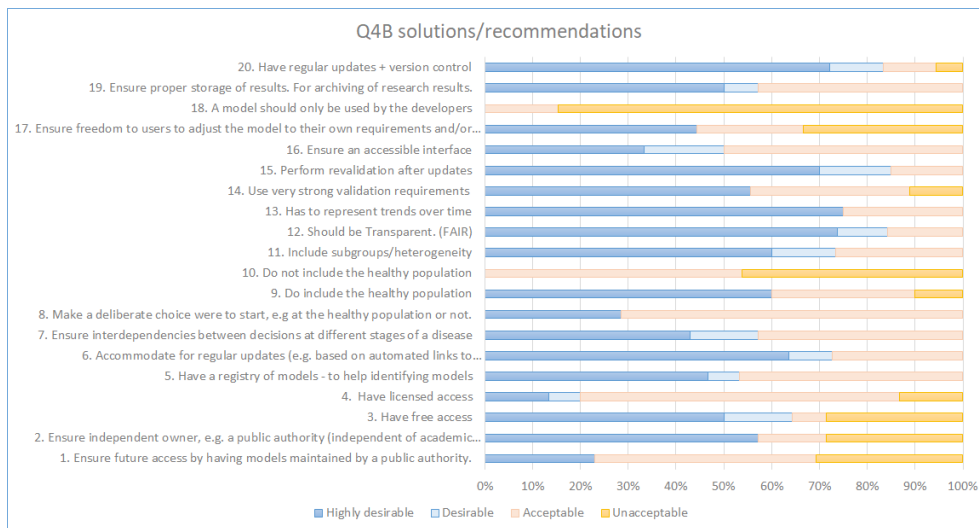

Figure 14 Solutions/recommendations of issues for multi-use disease models

Table 1 Complete table of issues, as suggested by the panel in round 1 and grouped by the team

Category	Issue/challenge/choice to be made
Organization (access & ownership)	1. Funding for maintenance
	2. Funding for hosting / Q&A to support users
	3. Ownership (model and results)
	4. Role of stakeholders
	5. Mandatory or optional use in policy contexts
	6. What kind of software is allowed or suitable (in relationship to accessibility/users/regulation)
	7. Liability agreement for wrong results (caused by wrong model)
	8. Prevent misuse (uniformed, inappropriate),
	9. Licensing + how to organize this
	10. How to ensure collaboration (synergy) between different research groups/ stakeholders
	11. Confidentiality agreement (e.g. a company using it on a drug in development)
Development of model	12. Consider a modular approach
	13. Model complexity/depth/degree of detail (balance specificity and generality)
	14. Should a multi-use model be an empty shell or a setting specific model
	15. Funding for development
	16. How to ensure sufficient transparency of model structure, assumptions and input data.
Input data.	18. To find an acceptable solution to the tension transparency & replicability versus privacy patient level data.
	18. When model is used repeatedly, and is based on patient level data, how is model use compatible with GPRD.
Validation and transparency	20. Communicating model limitations
	20. Risk in using one model structure; blinder for structural uncertainty;
	21. Comparability with other models or model outcomes
Model use.	23. Transferability (what part of a model is to be based on setting specific data?)
	23. How to ensure access to models for potential users., more practically
	24. Limits to acceptable run-time/software
Model results	26. Organize governance for access to model results of certain applications.
	26. How to improve model understanding (face validity, explanation)
Model maintenance (technical)	27. Should there be an 'official' (updated) version.
	28. How to have a sustainable knowledge base (expertise sits in humans) on the model including transparent documentation
	29. Ensure sufficient adaptability
	30. Time required to get approval for adaptations of the model
	31. Way of updating evidence that does not require adjustment of model structure (user interface)
	32. Way of updating evidence that would require adjustment of model structure

Table 2 Complete table of recommendations as suggested by the panel in round 1

Category	Recommendation
Organization (access & ownership) Money, legal, IP, etc.	1. Ensure future access by having models maintained by a public authority.
	2. Ensure independent owner, e.g. a public authority (independent of academic centers)
	3. Have free access
	4. Have licensed access
	5. Have a registry of models - to help identifying models
Development of model	6. Accommodate for regular updates (e.g. based on automated links to registries/claims data)
	7. Ensure interdependencies between decisions at different stages of a disease
	8. Make a deliberate choice were to start, e.g at the healthy population or not.
	9. Do include the healthy population
	10. Do not include the healthy population
	11. Include subgroups/heterogeneity
Input data	12. Should be Transparent. (FAIR)
	13. Has to represent trends over time
Validation and transparency	14. Use very strong validation requirements
	15. Perform revalidation after updates
Model use	16. Ensure an accessible interface
	17. Ensure freedom to users to adjust the model to their own requirements and/or data
	18. A model should only be used by the developers
Model results	19. Ensure proper storage of results. For archiving of research results.
Model maintenance (technical)	20. Have regular updates + version control

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