Point-by-Point Response

Stakeholder Comments for Scoping Document

Clinical Effectiveness, Safety and Cost-Effectiveness of Docetaxel, Abiraterone, Enzalutamide, Apalutamide or Radiotherapy plus Androgen Deprivation Therapy versus Androgen Deprivation Therapy Alone in Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer

commissioned by the Swiss Medical Board (SMB)

Assessment Team

Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zurich

European Center of Pharmaceutical Medicine (ECPM), University of Basel

13 March 2020

(First version: 15 November 2019)

Stakeholder Comments - Scoping SMB Prostate Cancer Drugs Project

Full name	**Bernhard Güntert**
Job title	Projektleiter Qualität und HTA
Organization	**curafutura**
Date	28.10.2019

Comment number	Chapter	Comment	Suggested change	Response
General Comments				
1		Grundsätzlich begrüsst curafutura das im Scoping-Bericht vorgeschlagene differenzierte Studiendesign. Auch ist die Relevanz für Versicherer gegeben. Als Problem sehen wir allerdings, dass es schwierig werden dürfte, die benötigten Informationen für diese differenzierte Analyse in der heute bestehenden Literatur mit der notwendigen Evidenz zu finden.		Vielen Dank für Ihre detaillierten Kommentare. Die zu erwartende Datenlage war ein wichtiger Diskussionspunkt im Entwurf dieses Projekts. Sicherlich werden nicht umfassende Daten für alle geplanten Analysen vorliegen. Dies ist aber gemäss unserer Sicht für kaum ein Krebsmedikament von aktuellem Interesse der Fall. Wir gehen davon aus, dass wir mit diesem Themengebiet einen Kontext mit einer vergleichsweise hohen Datenverfügbarkeit gewählt haben, welche auch einen interessanten Vergleich von neueren und älteren Therapien geben kann.

Specific Comments				
2	Subgroups p 8	Wir sind eher skeptisch, dass genügend aussagekräftige Daten für alle diese Subgruppen zur Verfügung stehen. Es dürfte auch sehr schwierig werden, anhand der Kriterien diese Patienten in den heterogenen Studien zu identifizieren		Vermutlich werden stratifizierte Daten nicht für alle Subgruppen, Behandlungen und Outcomes vorliegen. Für die meisten Studien liegen aufgrund der klinischen Relevanz allerdings stratifizierte Sekundäranalysen zu den genannten Subgruppen vor, zumindest für *overall survival*.
3	Data extraction p 10	Dass die Daten eines Trials über verschiedene Publikationen hinweg abgeglichen werden sollen ist positiv. Die Verwendung von RoB 2 wird begrüsst.		Danke.
4	Data analysis p 10	Die geplante Network meta-analysis ist nicht trivial. Wir empfehlen, dabei auch die Kommentare in der beiliegenden Studie zu berücksichtigen.		Es ist korrekt, dass die network meta-analysis (NMA) nicht unkompliziert ist. Leider werden uns für dieses HTA keine individuellen Patientendaten für eine komplexere Analyse vorliegen. Unterschiede in Studienpopulationen müssen sicherlich beachtet und der potentielle resultierende Bias mithilfe adäquater Methoden reduziert und in Sensitivitätsanalysen exploriert werden. Diesbezüglich ist ein detaillierteres Projektprotokoll in Bearbeitung. Wir möchten hierbei zudem erwähnen, dass es am EBPI eine starke Expertise in der Durch-führung von NMA gibt.

5	Table 2 Agular et al. (30), p 13	Hier ist nicht nachvollziehbar, weshalb Abi+ADT vs Doc+ADT nicht CE sein so. Bitte nochmals verifizieren!		In der Studie von Aguiar 2019 war der Vergleich (ICER) von Abi+ADT, sowie Doc+ADT im Vergleich zu ADT alleine kosteneffektiv. Abi+ADT ist allerdings verglichen mit Doc+ADT bei einem ICER von CHF 140'284/QALY nicht kosteneffektiv (zumindest gemäss der Definition der meisten Gesundheits-systeme (WTP ≤100'000 CHF)).
6	Cost-effectiveness analysis p 14	Es dürfte schwierig werden, bei dieser kleinen Anzahl von (heterogenen) Studien eine valide Aussage zu machen!		Wir hoffen, dass uns die Datenlage erlauben wird, eine *de novo* Kosteneffektivitätsanalyse für die Schweiz durchzuführen. Welcher Detailgrad dabei aufgrund vorliegen-der Daten möglich ist, wird sich herausstellen. Wir gehen aber davon aus, dass zumindest für Docetaxel und Abiraterone genügend Daten für eine solche Analyse vorliegen. Dies könnte selbst im Falle fehlender Daten für die anderen Behandlungen gewisse Rückschlüsse erlauben. Zudem ist anzumerken, dass für die Nutzen-Schaden Analyse abgesehen von den zu erwartenden Behand-lungseffekten insbesondere auch die Basisrisiken wichtig sein werden. Daher werden wir im geplanten HTA auch Evidenz aus observationellen Studien und Registern hinzuziehen.

7	Additional data source p 15	Genügen die stationären Daten? Vor allem Abiraterone wird doch häufig in der ambulanten Versorgung verwendet (müsste also über Tarmed identifiziert werden).		Es ist korrekt, dass einige der Behandlungen auch häufig im ambulanten Setting stattfinden. Wir werden, wo nötig, auch die ambulante Vergütung mit einbeziehen. Das Dokument wurde entsprechend angepasst.
8	Complementary elements p 17	Hier wäre es u.E. wichtig nicht nur die Patientenpräferenzen zu erfassen, sondern auch die Behandlungspräferenzen der betreuenden Onkologen		Die Behandlungspräferenzen der betreuenden Ärzte spielen nachgewiesenermassen eine nicht unerhebliche Rolle. Somit wäre Ihr Vorschlag durchaus sehr interessant. Im Rahmen dieses HTA ist ein solcher zusätzlicher Survey allerdings leider nicht realisierbar.

Stakeholder Comments - Scoping SMB Prostate Cancer Drugs Project

Full name	**Dr. Marianne Eggenberger**
Job title	Projektleiterin Medikamente
Organization	**santésuisse**
Date	29.10.2019

Comment number	Chapter	Comment	Suggested change	Response
General Comments				
1	Rationale (S. 2-5)	Das vorgeschlagene HTA soll sich auf die Indikation “neu diagnostiziertes metastasiertes Prostatakarzinom (mHSPC)” beschränken. Heute sind die neueren und verfügbaren Substanzen (Abirateron, Enzalutamid) jedoch nicht oder nur eingeschränkt für diesen Einsatz zugelassen und bezahlt. Oder sie sind im nicht metastasierten Setting gemäss FI vorgesehen (Apalutamid) und durch die OKP (noch) nicht vergütet. Es scheint daher nicht gänzlich nachvollziehbar, warum das HTA sich einzig auf die neu diagnostizierten Prostatakarzinome beziehen soll, zumal zukünftig und erwartungsgemäss gerade die Frage der Therapiefolge relevant sein wird.	Es wird vorgeschlagen, die Fragestellung dahingehend auszuweiten, dass auch die Relevanz neuerer Therapien bei Progredienz nach Behandlung mit Docetaxel einbezogen wird. Dies auch im Hinblick, als keine entsprechende Indikation in der Schweiz in dieser Form vorliegt und damit auch eine reguläre Vergütung durch die OKP in der vorgesehenen Indikation nicht möglich ist. Dies auch wenn der heute eingesetzte Standard nicht gänzlich dieser Therapiefolge entspricht.	Vielen Dank für Ihre wertvollen Kommentare. Die Therapiefolge ist tatsächlich von hohem Interesse. Zur optimalen Sequenz liegen allerdings noch kaum Studiendaten vor. Da die Daten für Enzalutamide und Apalutamide im Kontext von mHSPC erst kürzlich publiziert wurden, gehen wir von einer Indikationserweiterung und Änderung der Vergütung im Verlauf des nächsten Jahres aus. Eine zusätzliche Ausweitung der Fragestellung dieses ohnehin schon aufwändigen Projekts auf *second line* Therapien ist leider nicht realisierbar. Wir erachten den gewählten Kontext (mHSPC) als besonders relevant, da dieser die grösste Patientengruppe abbildet und damit den höchsten *cost*

				und *symptom burden* hat. Zudem stellt sich gerade in diesem Gebiet aktuell die Frage nach der Äquivalenz der neuen Behandlungen bezüglich ihrer Wirksamkeit und Nebenwirkungen. Wir gehen davon aus, dass die Benefit-Harm- und Kosteneffektivitäts-Analysen einige Aufschlüsse über eine optimale Sequenz aus patienten-zentrierter (klinischer) und ökonomischer Sicht liefern werden.
2	Decision Context – Population S. 6	Patienten, welche vorgängig Docetaxel erhalten haben, werden ausgeschlossen. Wie auch oben bereits ausgeführt, sollten gerade auch diese Patienten mitberücksichtigt werden.	Es wird vorgeschlagen, auch Patienten mit einer Docetaxel-Vortherapie miteinzubeziehen (siehe auch Pkt. 1), um insbesondere auch den heutigen, durch die Zulassung beschränkten Einsatz abzubilden.	Wir haben diesen Punkt nochmals evaluiert, sind aber zum Schluss gekommen, dass wir in diesem Projekt nur *first line* Therapien berücksichtigen können.
3	Decision Context – Population S. 6	Studien, welche mehr als 10% von Patienten enthalten, die eine seltene Form des Prostatakarzinoms haben, sollen ausgeschlossen werden. – Dieser bereits vorgängig definierte Ausschluss kann nicht nachvollzogen werden. Grundsätzlich sollten alle Studien miteinbezogen werden, insbesondere auch solche mit seltenen Formen, wo diese mit einer signifikanten Zahl von Patienten mögliche und nachvollziehbare Daten liefern.	Es wird vorgeschlagen, auch Studien miteinzubeziehen, die eine grössere Zahl von Patienten mit seltenen Formen von Prostatakarzinomen einbezogen haben. Damit werden auch mögliche Subpopulationen allenfalls sichtbar, die von einer anderen Therapie als im Allgemeinen profitieren und die entsprechenden Therapien einen anderen Stellenwert erhalten.	Sicherlich ist die Subgruppe mit *aggressive variant (neuroendocrine) prostate cancer* interessant. Diese Patienten benötigen aber vermutlich gänzlich andere Chemotherapie-Schemata, weshalb wir sie in diesem HTA nicht zusätzlich berücksichtigen können. Unseres Wissens sind aus den aufgeführten Studien keine Subgruppenergebnisse für solche Patienten verfügbar.
4	Decision Context –	Es wird begrüsst, dass auch Apalutamid in das HTA einbezogen wird, obwohl dessen Zulassung nicht	Warum und welche Form von Studien mit Bicalutamid (und Flutamid (aH)) ausgeschlossen werden, soll klarer	Wir haben das Dokument in dieser Hinsicht revidiert. Bicalutamid und Flutamid (sowie andere non-steroidale

	Intervention S. 6-7	im metastasierenden Setting des Prostatakarzinoms erfolgte. – Gleichzeitig werden Interventionen ausgeschlossen. Dazu gehört gemäss Liste u.a. Bicalutamid. Auch wenn das Produkt älteren Datums ist, ist unklar, welche Studien mit Bicalutamid ausgeschlossen werden sollen. Umsatzzahlen zeigen heute, dass diese Substanz noch immer eingesetzt wird.	ausformuliert werden. Es darf nicht dazu führen, dass wichtige Studien grundsätzlich dadurch ausgeschlossen werden und damit die Beantwortung der vorliegenden Fragestellung im heutigen Umfeld geschwächt wird.	Antiandrogene der alten Generation) haben gemäss der involvierten klinischen Experten kaum Stellenwert in der heutigen Praxis. Wir werden diese daher nicht separat als Intervention untersuchen. Patienten in den Kontrollgruppen der Studien dürfen im Rahmen des aktiven Komparators solche Medikamente erhalten haben.
5	Comparator S. 7	Als Komparator wird einzig ADT alleine (oder mit Placebo) zugezogen. Unter der Kosten-Nutzen-Analyse wird jedoch ein Hinweis gemacht, dass Abirateron im Vergleich zu Docetaxel (jeweils zusammen mit ADT) nicht kosteneffektiv war.	Es wird vorgeschlagen, bereits hier einen Vergleich der neueren Therapien kombiniert mit ADT versus nicht nur gegen ADT sondern auch gegen Docetaxel kombiniert mit ADT zu berücksichtigen – um diesem Aspekt später in der Analyse ausreichend Rechnung tragen zu können.	Die geplante HTA sieht vor, sowohl Abi+ADT, Enz+ADT, Apa+ADT, wie auch Doc+ADT als "experimentelle Interventionen" zu untersuchen. Gemäss der Rückmeldungen der klinischen Experten werden wir zudem Radiotherapie+ADT mit einbeziehen. Für jede oben genannte Therapie gehört dazu der Vergleich gegen ADT ("aktiver Komparator"), sowie indirekt gegenüber der anderen Behandlungen (d.h. auch gegen Doc+ADT für die neueren Hormontherapien).
6	Study Designs S. 8	Grundsätzlich werden nur RCT für die Beurteilung der Wirksamkeit und Sicherheit der Produkte berücksichtigt. Auch wenn erwartet werden kann, dass Docetaxel und Abirateron mit verschiedenen Studien untersucht wurde, sollten weitere Studienformate (Beobachtungen, Register etc.) nicht grundsätzlich ausgeschlossen werden.	Es wird vorgeschlagen, nicht grundsätzlich für die Beurteilung der Wirksamkeit und Sicherheit nur RCT zu berücksichtigen. Insbesondere allfällige Register-Daten (wie unter Kapitel BHA erwähnt) oder auch Beobachtungsstudien sollten auch in diesem Bereich zumindest für mögliche Hinweise genutzt werden.	Wir haben auch diesen Punkt nochmals evaluiert. Gemäss einer kurzen preliminären Suche gibt es nur wenige Beobachtungsstudien von eher kleiner Grösse in diesem Kontext (n<200). Zur Beurteilung der Wirksamkeit der Therapien sehen wir daher hauptsächlich die randomisiert-kontrollierten Studien (RCTs) als

		Sie können durchaus wichtige Hinweise zu entsprechenden Therapien, u.a. angewendet im alltäglichen Setting liefern.		ausschlaggebend. Selbstverständlich werden wir aber auch Evidenz aus observationellen Studien und Registern berücksichtigen, sofern wichtige Kriterien erfüllt sind (siehe Cochrane Handbook Kapitel 24). Solche Evidenz ist zudem für die Durchführung der Nutzen-Schaden Analyse unerlässlich. Resultate zur klinischen Wirksamkeit und Sicherheit werden im Kontext der gesamten verfügbaren Evidenz diskutiert werden.
7	Subgroups of Interest (S. 8)	Es werden diverse Subgruppen aufgeführt – sofern genügend Daten vorliegen.	Wie bereits unter Pkt. 3 dargelegt, schlagen wir vor, grundsätzlich keine Subgruppen (z.B. seltene Formen von Prostatakarzinomen) auszuschliessen, sofern für eine Beurteilung und im Vergleich ausreichend Daten vorliegen.	Die *subgroups of interest* umfassen die im Voraus geplanten Subgruppenanalysen. Diese entsprechen den Kategorien, welche in der Klinik relevant sind und sich auch in der Behandlungsindikation (gemäss Fachinformation) wiederspiegeln. Der Ausschluss der *aggressive variant prostate cancer* ist oben diskutiert.
Specific Comments				
8	Part I: Current Evidence (S. 8)	Gemäss Tabelle 1 wurden bis anhin rund sieben durchgeführte Studien gefunden, deren Resultate in verschiedenen Publikationen zugänglich sind. Das weitere Vorgehen und die aufgeführten verschiedenen Datenbanken und Grundlagen für die systematische Review sind nachvollziehbar. Es wird begrüsst, dass insbesondere bereits existierende Metaanalysen und	Auf Grund der geringen Anzahl an Studien erachten wir es als sinnvoll, nicht nur RCT einzubeziehen, sondern wie unter Pkt. 7 bereits ausgeführt auch weitere Studien zumindest in Erwägung zu ziehen (Beobachtungsstudien etc.). Es wird auch als wichtig erachtet, heutige und existierende Leitlinien zu berücksichtigen, welche im	Wie in Punkt 6 diskutiert, erwarten wir von den observationellen Daten hinsichtlich der Wirksamkeit kaum ausschlaggebenden Einsichten. Die sieben RCTs sind adäquat gepowered und stellen im Bereich von innovativen Krebstherapien sogar eher eine starke Evidenzlage dar. Selbstverständlich werden unsere Resultate auch im Kontext der existierenden Leitlinien, Konsensusprozesse und verfügbaren

		systematische Reviews miteinbezogen werden sollen. Grundsätzlich sind es aber lediglich sieben Studien, welche zu Docetaxel und den neueren Substanzen durchgeführt wurden.	vorliegenden Scoping nicht speziell erwähnt wurden.	Beobachtungsstudien analysiert und diskutiert werden.
9	Part I: Data Analysis S. 10 – 11	Wie bereits unter Pkt. 1 und 2 ausgeführt, wird eine Ausweitung der Fragestellung zusätzlich auf Therapien u.a. nach Docetaxel vorgeschlagen. Damit würde sich die Figur zusätzlich erweitern.	Es wird vorgeschlagen, auch die Therapielinie mind. nach Docetaxel zu beurteilen, allenfalls sogar allgemein die heutige Therapieevidenz in zweiter/dritter Linie.	Wie vorgehend dargelegt, können wir *second* und *third line* Therapien leider nicht mit ins HTA einbeziehen.
10	Part II: Brief overview S. 12 – 13	In einer ersten Analyse wurden 11 Studien gefunden, welche eine cost-effektiveness-Analyse adressierten. Dabei zeigt eine Studie, dass Kosten-Nutzen von Abirateron versus Docetaxel, jeweils kombiniert mit ADT nicht besteht. Dies scheint uns ein interessanter aber auch wichtiger Hinweis zu sein.	Um dem interessanten Aspekt im HTA ausreichend Rechnung zu tragen, sollte aus unserer Sicht zumindest im Bereiche der Kosten-Nutzen-Analyse auch ein Vergleich der neueren Produkte versus Docetaxel stattfinden.	Wir sehen die vorliegenden Studien ebenfalls als interessante Evidenz, wobei diese selbstverständlich im Kontext des jeweiligen Gesundheits-systems zu interpretieren sind. Sofern durchführbar, planen wir durchaus eine komparative Evaluation der Kosteneffektivität aller möglichen Behandlungen im Kontext der Schweiz.
11	Part II: Approach to health economic assessment S. 13 – 15	Das Kapitel zeigt nachvollziehbar das Vorgehen für die Kostenanalyse auf. Dabei sollen Literatur-Reviews wie auch eine Cost-effectiveness Analyse und Budget-Impact Analyse diesem Aspekt Rechnung tragen. Dieses Vorgehen unterstützen wir sehr.		Danke.
12	Part III: Benefit-Harm Assessment	Mit diesem HTA soll ein BHA integriert werden, was auch durch andere HTA-Institutionen gefördert und verfolgt wird. Wir erachten dies als einen		Danke. Wir hoffen ebenfalls, durch die quantitative Benefit-Harm-Analyse zusätzliche wichtige Einblicke für eine patienten-zentrierte Therapiewahl zu

	(BHA) S. 16 – 17	potentiell wichtigen und spannenden neuen Ansatz, insbesondere auch im vorliegenden HTA zum Prostatakarzinom. Gerade die neueren Substanzen wie Abirateron oder Enzalutamid zeigen ein ausgeprägtes Nebenwirkungsprofil, das nicht zu unterschätzen ist und ein wichtiger Aspekt bei der Beurteilung über den adäquaten Zeitpunkt des Einsatzes ist (1st-Line, 2nd-Line etc.). Der hier verfolgte quantitative Ansatz könnte hier im Speziellen zusätzliche Informationen liefern.		gewinnen. Dies könnte u.a. auch für die Wahl der Therapiesequenz von Relevanz sein.
13	Expected Impact S. 17 – 18	Wie vermerkt wird, soll das vorliegende HTA helfen, die Therapie des fortgeschrittenen, metastasierende Prostatakarzinoms (mHSPC) im Speziellen in der ersten Linie mit älteren aber auch neueren Substanzen zu bezeichnen.	Wie bereits unter Pkt. 1 vermerkt, erachten wir es als wichtig, auch die Indikation in der zweiten und folgenden Linie u.a. nach Docetaxel) beim mHSPC zu berücksichtigen und mit diesem HTA zu adressieren. Die neuen Substanzen Abirateron und Enzalutamid sind insbesondere nach Progress unter Docetaxel zugelassen und durch die OKP vergütet. Eine wichtige Frage daher für die Behörden über eine Vergütung in der ersten Linie (sofern zugelassen) zu beschliessen ist die Einordnung in der Therapielinie (Zweckmässigkeit).	Wie unter Punkt 1 ausführlich diskutiert, erachten wir die Frage nach der Therapiesequenz ebenfalls als sehr wichtig. Leider ist es im Rahmen dieses HTA und basierend auf der aktuellen Datenlage nicht möglich, eine solche umfassende und detaillierte Analyse durchzuführen. Wir gehen aber davon aus, dass unsere Resultate dennoch massgebliche Einsichten liefern wird, welche auch für die Festlegung der Therapie-sequenz von Relevanz ist.
Fazit				
Der hier vorgelegte Scoping-Bericht adressiert die Fragestellung der heutigen Therapie von Patienten mit neu diagnostiziertem, metastasierendem Prostatakarzinom (mHSPC). Es wird nachvollziehbar aufgezeigt, welche				Vielen Dank für Ihr positives Feedback.

Informationen zur Wirksamkeit aber auch zur Wirtschaftlichkeit nach einer ersten Recherche vorliegen. Gleichzeitig werden das weitere Vorgehen und die geplanten Schritte für ein Full-HTA beschrieben. Die heute eingesetzten und neueren Produkte Abirateron und Enzalutamid sind primär in der zweiten Linie nach Progress unter Docetaxel beim mHSPC zugelassen und durch die OKP vergütet. Es scheint uns daher ein wichtiger Aspekt zu sein, auch den heutigen Einsatz der neueren Produkte nach regulatorischen Vorgaben zu berücksichtigen. Eine entsprechende Ausweitung der Fragestellung wäre daher zu begrüssen. Dass nebst dem Health Economic Assessment auch ein Benefit-Harm Assessment geplant und durchgeführt wird, begrüssen wir sehr. Wir sind auf die daraus resultierenden Daten gespannt. Auf Basis aller im Scoping-Bericht zusammengestellten Daten ist santésuisse der Meinung, dass ein Full-HTA vielversprechend ist. Die Durchführung eines Full-HTA wird somit von santésuisse begrüsst und unterstützt.	

Stakeholder Comments - Scoping SMB Prostate Cancer Drugs Project

Full name	**Leila Baumann**	**Patrick Adorjan**	**Verena Doye**	**Aurea Dura**
Job title	Associate Director Market Access & Government Affairs	Associate Medical Affairs Director Oncology	EMEA Market Access Director	HEOR Associate Director
Organization	**Astellas Pharma AG**	**Astellas Pharma Europe Ltd**	**Astellas Pharma Europe Ltd**	**Astellas Pharma Europe Ltd**
Date	29.10.2019			

Comment number	**Chapter**	**Comment**	**Suggested change**	**Response**
General Comments				
1	Rationale	The number of listed treatment available including Docetaxel, Apalutamid and Enzalutamid are not approved by Swissmedic for the treatment of mHSPC. Therefore, non these substances have undergone a price evaluation by the Federal Office of Public health. To include these products in a cost-effectiveness modelling with prices based on the current price levels in the speciality list will lead to a bias in the outcome of cost-effectiveness.	The HTA should be postponed and conducted after Swissmedic approval of Apalutamid and Enzalutamid for mHSPC and the reimbursement process for mHSPC has been performed by the Federal Office of public health. Given the generic status of Docetaxel, it is doubtful that a label change to add mHSPC to the Docetaxel label will be submitted to Swissmedic (According to available information, no label change has been requested in 2019). Only prices assessed by the FOPH in a regular reimbursement process reflect the value of the products for the treatment in mHSPC.	Thank you very much for your valuable comments. Docetaxel is commonly used *off-label* in mHSPC. While a label change is not currently to be expected, the fact that an effective generic treatment is not approved may highlight a weakness in the Swiss system of pharmaceutical approval. Both Enzalutamide and Apalutamide are expected to be approved for this indication within a reasonable timeframe, potentially before the completion of this project. It is not the purpose of this HTA to interfere with the regular reimburse-ment process of the Federal Office of Public Health as laid out by the law. This independent HTA project aims to explore the area of novel cancer drugs

				in a Swiss context and to derive recommendations for the treatment of mHSPC. Recommendations by the Swiss Medical Board are non-binding by nature, and it is at the discretion of the FOPH whether to consider the findings of this project.
2	Rationale, page Nr. 4 paragraph 1	It is mentioned that only Abiraterone and Docetaxel are approved for use in practice by Swissmedic. This information is incorrect as Docetaxel is only approved for Castration resistant prostate cancer and not mHSPC.	Correct statement according to approved indication. Only Abiraterone is approved by Swissmedic for the treatment of mHSPC even though in clinical practice Docetaxel is often used outside of its approved label.	Thank you for this correction. We changed the document accordingly.
3	Rationale, page 4, paragraph 2	The scope of the HTA within a feasible range given the timeframe and as this HTA is aimed at specifically exploring the area of novel cancer drugs, ..	To include Docetaxel, as highlighted in the previous paragraph to be a generic drug, is contradictory to the statement, that the aim is to explore the area of novel cancer drugs.	We agree that it may seem contra-dictory to include older treatments in this HTA under this perspective. However, we consider it a strength of the project that it may allow a comparison between older (generic) and newer drugs used in mHSPC.
4	Rationale, page 5	It is stated that newer drugs incur much higher costs to healthcare systems and patients.	As previously mentioned Apalutamide and Enzalutamid are not yet approved for mHSPC in Switzerland. In addition, no price evalutation for nmCRPC has been conducted for Apalutamide and therefore at current date, no price level for Switzerland is available for Apalutamide. The statement, that newer drugs incur much higher costs to the healthcare system can only be assessed for substances approved	We acknowledge that this statement in the context of the paragraph is mis-leading. We adapted it accordingly.

			and reimbursed by the Federal Office of Public health.	
5	Rationale, Page 5	Treatment costs and therefore reimbursement authorities and regulatory systems have to be strictly distinguished.	It is not within the scope of a regulatory body like the FDA, EMA or Swissmedic to establish the cost-effectiveness or treatment costs of new drugs to be approved. A regulatory approval of a new substance is solely based on clinical efficacy and safety. Reimbursement authorities like NICE and the FOPH are assessing the costs of new treatments and determine a country specific price level at which the treatment is considered economically viable. Findings of country specific authorities cannot be conveyed 1:1 to other countries due to different health insurance systems. The process of reimbursement for new drugs and new indications is in Switzerland defined by law and follows the same procedure independent of therapeutic area or size of the treated patient population. As a consequence, the cost-effectiveness and budget impact evaluation should be excluded from this HTA. There is no legal ground to determine the cost-effectiveness of cancer drugs in Switzerland based on an HTA and recommendations	We agree that the assessment of novel drugs by regulatory bodies should primarily be based on the clinical efficacy and safety. This needs to be distinguished from the process for determining eligibility for reimbursement and price, which requires a systematic HTA and for which the FOPH is responsible. We also agree that caution needs to be applied when interpreting cost-effectiveness analyses conducted in other contexts. It is thus essential to thoroughly assess the transferability of findings to the context of Switzerland. However, we do not see a reason not to conduct a cost-effectiveness and budget impact analysis based on these considerations. Economic evaluations are a standard component of HTA (please see EUnetHTA) and give important insights on the economic viability of a treatment. While processes for reimbursement in Switzerland are standardized and have to take place in accordance with the prevailing law, an economic evaluation of the treatments will still be a useful addition to inform the national discussion and enrich the international scientific literature. This will also allow

			regarding cost-effectiveness cannot be binding in regards to the reimbursement of these drugs in Switzerland. Only drugs that have undergone the official reimbursement procedure for which the Federal Office of Public Health alone is in charge, are covered by the mandatory health insurance and reimbursed for the treatment of mHSPC.	us to highlight difficulties that we may encounter when conducting such an analysis for Switzerland. From this, recommendations may arise for improving and streamlining drug reimbursement assessment for cancer drugs in Switzerland, thereby equally benefiting the FOPH, insurers, the pharmaceutical industry, and - most importantly - patients in Switzerland.
6	Rationale, Page 3	Both enzalutamide and apalutamide showed promising results on progression-free survival in early analyses [12–14]	Both showed OS benefit in early analyses and not only PFS. Please see ENZAMET and TITAN	Please apologize this unintentional omission. We adapted the document accordingly.
7	Objectives, Page 5	Assess adverse events and toxicity of the different treatment options	Including appendix search for each publication	We consider it good research practice to include all evidence, including the appendix of published studies in the analysis. To the extent that the data accessible to us allows, we will strive to include the most applicable and valid (subgroup) evidence for each analysis.
8	Intervention, Page 6	Hormonal therapy with first-generation non-steroidal androgen-receptor antagonists, such as bicalutamide or flutamide	It is not clear if the agents that are excluded are also excluded from being an active comparator. If so, it would mean that in the network meta-analyses the active control arm of ENZAMET will be excluded.	We agree and adapted the research protocol accordingly. First-generation non-steroidal anti-androgens will be considered eligible as an add-on to ADT in the active comparator group, but not separately examined as an experimental intervention.
9	Comparator, Page 7	ADT alone or in combination with placebo, daily oral medication (standard dose)	And to include ENZAMET in the analyses, the comparator should also be ADT and NSAA	Please see comment 8.

10	Study design, Page 8	Evidence from RCTs...	Is the study design also including flagship RCT as in STAMPEDE? If yes, then to mention it. For example, how to compare the inclusion and exclusion criteria of STAMPEDE with RCTs such as TITAN, ARCHES and ENZAMET? This should also be mentioned.	Multi-arm multi-stage platform trials, although not a "classical" RCT, will be considered eligible. We changed the wording accordingly. Information on study inclusion and exclusion criteria will be extracted from study reports and protocols, and baseline characteristics of trial populations will be assessed for comparability. This will be an essential component of the transitivity assessment in the network meta-analyses. The more detailed methodology will be addressed in the study protocol.
11	Figure 1, Page 11	ADT+Enz	If exclusion criteria of the Network meta-analyses includes NSAA, how can we compare within the network analyses ADT and ENZA vs ADT and NSAA?	Please see comment 8.
13	General comment	Network meta-analysis, Chaarted, Latitude and Stampede have 100% study patients that fit with inclusion criteria vs 50%		Please see comment 10.
14	Page 3, Davis 2019		For all publications, appendix should be included in the publications for the network meta analyses. Adverse events profile and further stratifications, eg Enzalutamide without docetaxel in OS and clinical progression free survival are only addressed in the appendix and not in the primary manuscript.	Please see comment 7. We will consider evidence for the appropriate subgroup wherever data is published or otherwise accessible to us. Thank you for pointing this out.

			AEs in the main publication include the overall population (with or without docetaxel, and this might be misinterpreted if not yet based on the HTA protocol). This may be relevant for the BHA part III of this protocol.	
Specific Comments				
Timeline on data availability		ARCHES: per protocol there is no further interims analyses planned, only final analysis. Estimated Study Completion Date December 2023		This is congruent with our understanding.
Patient population differences	In general, the comparison of results across studies is limited by the differences in composition of study patient populations, trial designs and time of follow-up			It will certainly be a limitation of this project that the patient populations between the relevant studies are different with respect to some key variables. Detailed methods for exploring heterogeneity in study populations and implications for transitivity in network meta-analysis will be elaborated and specified in more detail in the research protocol. Unfortunately, it is highly unlikely that we will be able to access individual patient data (IPD) for any of the studies. This would allow us to conduct more complex analyses and better account for such population differences. Of course, we would be very happy to discuss IPD access, if data sharing is something Astellas Pharma considers possible for the studies in question.
	% mHSPC	Chaarted, Latitude, Arches, Enzamet and Titan have 100% mHSPC patients vs Stampede arm C with 62% and Stampede arm G with 52%.		
	% de novo metastatic disease	Latitude has 100% de novo metastatic disease patients, Stampede arm G 95%, Titan 78%, Chaarted 73%, Arches 70%, Enzamet 60% and Stampede arm C 59%	Comment: Lower de novo metastatic disease in Enzalutamide trials vs Abiraterone trial	
	% recurrent disease	Arches has 30% of recurrent disease patients, Chaarted 27%, Titan 16%, Enzamet 15%, Stampede arm G 4% and Stampede arm C 3%	Comment: Exclusion criteria, these patients will be excluded.	
	% low risk/volume patients	Most low risk/volume patients are in Enzamet 48%, less in Arches and Titan with 38% each, and 34% in Chaarted. Stampede arm C, G and Latitude have none of these patients		

	% high risk/volume patients	Latitude has 100% high risk/volume patients, Chaarted 66%, Arches and Titan 62%, Enzamet 52% and no high risk/volume patients in Stampede arms C and D		
Trial design differences	% prior Docetaxel use	18% of patients in Arches and 17% in Enzamet had prior Docetaxel use, 11% in Titan and none in the other mHSPC trials Chaarted, Latitude and Stampede arms C and G	Comment: Abiraterone without prior Docetaxel use, with Enzalutamide 35%. Unbalanced patient population comparison.	A priori and if feasible in any way given the accessible data, we will exclude the subgroup of patients that have received a novel hormonal therapy as a *second line* treatment.
	% of concurrent Docetaxel use	45% of patients in Enzamet had concurrent Docetaxel use, none in the other mHSPC trials Latitude, Titan and Stampede arm G	Comment: 55% patients in Enzamet received Enzalutamide and ADT without Docetaxel, which shows 54% risk reduction of death compared to the overall population.	We will also include treatment combinations (such as concurrent use of chemotherapy and enzalutamide), as far as available data allow. We have changed this in the scoping document (Decision Context / PICO).
Follow up (months)		Latitude study has longest follow-up with 52 months, Stampede 40 months, Enzamet 36 months, Titan 23 months and Arches 14 months		Methods to deal with differences in follow-up are currently being elaborated and will be specified in the research protocol.

Stakeholder Comments - Scoping SMB Prostate Cancer Drugs Project

Full name	**Sraboni Ghose**
Job title	Medical Scientific Liaison, Stv. FvP
Organization	**Ferring AG**
Date	29.10.2019

Comment number	Chapter	Comment	Suggested change	Response
General Comments				
Specific Comments				
1	Rationale	The list of relevant RCTs is not complete.	Table 1 page 3, consider adding PEACE1 trial (NCT01957436)	Many thanks for your comment. The PEACE1 trial was not included in the table, as no results have yet been published. If trial results become available until the conduct of the analysis, these will be included in the HTA. Furthermore, we included radiotherapy+ADT as an experimental intervention according to the feedback by the involved clinical experts. We have adapted Table 1 accordingly.

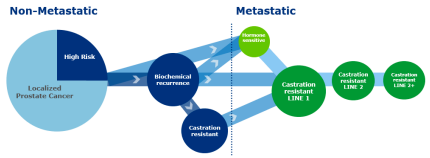
Stakeholder Comments - Scoping SMB Prostate Cancer Drugs Project

Full name	**Nadja Dibke-Steinmann**
Job title	Head Market Access & Pricing
Organization	**Janssen-Cilag AG**
Date	18.02.2020

Comment number	Chapter	Comment	Suggested change	Response
General Comments				
1	Process/ procedural	Several stakeholder groups are listed under the title section, however, which group was invited at what point in time and gave which input is not transparent	Add appendix to scoping document with a matrix of stakeholders that shows transparently their input and the timing of their input. Further add detail on why the respective input was or was not incorporated in the document.	Many thanks for your valuable comments. Due to technical communication issues, your company's feedback was unfortunately received rather late in the process of the HTA. For this reason, we were not able to incorporate all your comments. However, we made appropriate adaptations where possible at the current stage of research. The updated scoping document includes a list of all stakeholders involved in the scoping of the HTA. Furthermore, all received stakeholder comments including the point-by-point responses will be made public by the Swiss Medical Board. A more detailed stakeholder list, including information about stakeholder input/involvement

				at different project stages and timing of input will be added to the final HTA report.
2	Process/ procedural	Under the title section, pharmaceutical industry and specifically involved companies, i.e., Janssen, Astellas, Sanofi are stakeholders in this process but are not reflected	As pre above point, add stakeholder matrix and also include pharmaceutical industry as a stakeholder	Please see comment 1. The pharmaceutical industry and specifically the involved companies from which feedback was received have been included in the stakeholder list.
3	Across document	Inconsistent definition of the population to be considered by this appraisal The term “newly diagnosed” does not seem to be used consistently through-out the document and a precise definition is lacking. Further besides newly-diagnosed also “de novo” is used, which adds to further confusion	We would suggest in line with international consensus the following definitions: • mHSPC: all patients with metastatic, hormone sensitive prostate cancer • newly diagnosed mHSPC: Patients with metastatic, hormone sensitive prostate cancer whose first prostate cancer diagnosis is mHSPC, i.e., they did not have any previous local disease diagnosis • Primary progressive mHSPC: Patients with metastatic, hormone sensitive prostate cancer who have had previous (local) prostate cancer diagnosis and might have had several interventions to treat	In our view, the international literature does not use these expressions fully consistently. We use the following terminology used at the Advanced Prostate Cancer Consensus Conference (APCCC) 2019: • newly diagnosed mHSPC involves both patients with an initial diagnosis of mHSPC (i.e., *de novo* mHSPC), as well as patients with newly diagnosed mHSPC relapsing after local treatment of the primary tumor (i.e., progression after prior local therapy). We have specified this more clearly in the scoping document. We have adapted the wording of the risk categories according to the definition of the LATITUDE study.

			local disease, i.a., ADT, prostatectomy, etc. • High risk mHSPC (as per LATITUDE study criteria): at least two of the three high-risk prognostic factors, i.e., Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis except lymph node metastasis • Low/high volume disease: We recommend not to distinguish between high and low volume disease, as resent data from the STAMPEDE trial has called into question the relevance of disease volume.	The subgroup analyses by low/high volume category (as per CHAARTED study) were prespecified in our research protocol. This distinction has been a recurrent discussion in the context of mHSPC and has been postulated as a basis for decision-making (e.g., consensus for radiotherapy only in low-volume patients (see APCCC 2019)). While individual studies may not have found a difference between disease volume categories, there may be evidence for a difference (or no evidence for a difference) when combining data from multiple studies. Therefore, we consider the conduct of such subgroup analyses as justified.
Specific Comments				
4	Background, page 2	The report states the following: "*The Swiss Medical Board (SMB) plans to commission a health technology assessment (HTA) in the area of cancer drugs. The project intends to address current issues revolving around determining the value of novel cancer drugs and performing HTA in Switzerland in this context. By addressing a specific case example of high patient-level*	Address the issues of generalizability of the specifically chosen example for the "area of cancer drugs". We would recommend the following wording instead: "*The Swiss Medical Board (SMB) plans to commission a health technology assessment (HTA) in the area of cancer drugs. The project intends to produce a health technology assessment for Switzerland of a single and specific case that is both highly*	We agree that it is not possible to extrapolate from a single case example to the broader issue of addressing the value of novel cancer drugs. However, it is possible to highlight pertinent issues in the conduct of HTAs in the context of cancer drugs. We adapted the wording as follows: *"By addressing a specific case example of high patient-level and health system-level relevance, the*

		The extrapolation from a single, specifically selected case example to the broader issue of "determining the value of novel cancer drugs" is inadequate. The current scope does not allow the generalization of the learning from a specific case example to the value of cancer drugs overall.	*patient and system relevant. The HTA aims to have a two-fold impact […]"*	*HTA aims to have a two-fold impact: First, it will provide an up-to-date evaluation of the current evidence in a specific decision context, that will allow to derive treatment recommendations for patients in that situation. Second, the HTA seeks to explore current issues evolving around determining the value of novel cancer drugs and performing HTA in Switzerland in this context, and advance the area of HTA by providing additional scientific value with an impact on longer-term decision-making, HTA processes and/or value assessment in cancer care."*
5	Rationale, page 2	The different patient populations that are reported across this section and the corresponding incidence/mortality rates are not clearly separated and the data is not consistently reported. People unfamiliar with the matter might over/under estimate the unmet need and the size of the treated populations.	We would recommend including a visual, which shows the number of patients in each subgroup (incidence, prevalence rates) and the corresponding survival outcomes, e.g., 	We added a visual representation of patient trajectories to the document. The estimation of prevalence and incidence of mHSPC is one component of the health economic analysis. To our knowledge, these numbers are currently not readily available for Switzerland or reflected in the Swiss Cancer Registry. If such estimates are available for the pharmaceutical industry, we would highly appreciate if this data could be shared.
6	Rationale, page 2	The report states: *"These treatments are summarized under the term androgen deprivation therapy (ADT), which constitutes the mainstay of therapy for*	We would recommend the following wording: *"These treatments are summarized under the term androgen deprivation*	We adapted the wording according to your comment.

		prostate cancer patients in high risk localized as well as advanced (i.e. locally progressive or metastatic) disease stages" This statement is inaccurate since the use of ADT cannot be described as a mainstay and is sporadic in the high risk localized setting. ADT is specifically not recommended in EAU guidelines as neo-adjuvant to radical prostatectomy, and is uncertain as adjuvant	*therapy (ADT). In recent years, substantial advances have been made in the treatment of prostate cancer,"*	
7	Rationale, page 3	The report states the following: *"When added to ADT, both docetaxel and abiraterone demonstrated significant effects in prolonging overall survival [5–11],"*. In the publication by Gravis et al. the addition of docetaxel does not demonstrate a survival benefit in first line treatment for patients with non-castrate metastatic prostate cancer, compared with ADT alone. The report states the following: *"both enzalutamide and apalutamide showed promising results on progression-free survival in early analyses [12–14]."* Apalutamide has shown significant overall survival outcomes in its first interim analysis, not only PFS benefits.	We would suggest the following wording: "*When added to ADT, both abiraterone and apalutamide demonstrated significant effects in prolonging overall survival, while enzalutamide showed promising results on progression-free survival in early analyses. Adding docetaxel to ADT demonstrated significant effects in prolonging overall survival in most trials, however, the GETUG-AFU 15 trial failed to demonstrate a survival benefit for docetaxel [5–14]*	Please apologize this unintentional omission. We adapted the document accordingly.
8	Rationale, page 3	The report states the following: "*These effects may, however, depend on the volume and risk category of the disease,*	We recommend removing this sentence from the report	The sentence did not refer to the treatment with apalutamide, but rather to all the treatments of interest in the

		as well as whether mHSPC was diagnosed de novo (i.e., as the first diagnosis) or after prior local therapy (i.e., local treatment of the primary tumor)." Based on TITAN trial/publication, the treatment effect of apalutamide on rPFS is significant irrespective of volume disease.		HTA. We adapted the wording to clarify this.
9	Rationale, Table 1, page 3	There is ambiguity in the content of column 4 'details'. It is unclear what is meant by 'main analysis', early analysis', etc.	Add greater clarity to the content in column 4	We changed the content of column 4 to incorporate details on whether it constitutes a primary, long-term or other analysis, as well as on the follow-up time point of the respective publications. Furthermore, we have added some information about which of the core outcomes of the HTA are reported in the respective publication.
10	Rationale, Table 1, page 3		Add the following publications to the list as well: • James 2016 & Clarke 2019 for STAMPEDE DOC+ADT vs ADT • Hoyle 2019 full publication Add the following details for clarity: • ARCHES and TITAN are performed post docetaxel use (Y/N), while ENZAMET is plus deocetaxel (Y/N)	We adapted Table 1 according to our current knowledge of the evidence based on our scoping search. Compared to the previous version (dated 15 Nov 2019), we added the following publications: • Gravis 2016 for GETUG-AFU 15 • Hoyle 2019 (full publication) for STAMPEDE Abi • Agarwal 2019 for TITAN We further made minor corrections to: • James 2016 for STAMPEDE Doc (year of publication)

			• In LATITUDE all patients are de novo (i.e., newly diagnosed) and high risk	• Parker 2018 for STAMPEDE RTx (journal) And last, we added information on which trials included non-metastatic patients, were limited to de novo or high-risk patients, or included patients who received prior docetaxel or patients receiving concurrent docetaxel.
11	Rationale, page 3 Rationale, Table 1, page 3	The report states the following: *"Another matter of current debate is the optimal sequencing of treatments, for which randomized controlled trial (RCT) data are lacking."*. Trials for abiraterone and apalutamide (LATTIUDE, TITAN) have PFS2 data included. Those trials do not have formal re-randomization but give clear indications on success of subsequent treatments and hence the sequencing question	We would suggest adding the fact that PFS2 was captured in LATITUDE and TITAN to column 4 in table 1. We would further suggest the following wording in the text: *"Another matter of current debate is the optimal sequencing of treatments, for which randomized controlled trial (RCT) data are lacking, however, for both abiraterone and apalutamide data on PFS2 for various follow-on treatments are reported in the LATITUDE and TITAN studies, which give reliable insights on sequencing of treatments"*.	Thank you for raising the point that PFS2, or second progression-free survival, was reported in the LATITUDE and TITAN studies. PFS2 is recommended by EMA as addition to PFS if OS data are not available. PFS2 enables a controlled comparison of treatment arms if the subsequent treatment is prespecified. However, its interpretation may be complicated if treatment sequences are not incorporated in the study design. Thus, the reliability of insights on treatment sequences may be questionable. As we will discuss follow-up treatments in the HTA, PFS2 will also be considered in the discussion of the findings. However, given the limitations stated above, it will not be included as a critical or important outcome for the systematic review.

				Table 1 was changed More detailed information about the trials will be reflected in the HTA report.
12	Rationale, page 4	The report states the following: *"In Switzerland, only treatment with docetaxel and abiraterone (limited to high risk mHSPC) are currently approved for use in practice by swissmedic [20]".* Docetaxel is **not** indicated for hormone sensitive disease by Swissmedic The report states the following: *"Enzalutamide and apalutamide are pending approval by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in this indication."* Apalutamide is approved both by the FDA as well as the EMA	We would suggest the following wording: *In Switzerland, only treatment with abiraterone (limited to newly diagnosed and high risk mHSPC) is currently approved for use in practice by swissmedic. Docetaxel is only approved in the castration resistant setting and is therefore used in Switzerland in the mHSPC off-label [20]. Enzalutamide is approved in the US by FDA and pending approval by EMA: Apalutamide is approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in this indication."*	We adapted the document to reflect the current approval status for enzalutamide and apalutamide (as of 13 Mar 2020). The approval status of docetaxel was already corrected in a previous version (dated 15 Nov 2019).
13	Rationale, page 4, page 5	The report states the following: *"These innovative drugs compete with longer established chemotherapy, allowing treatment of patient groups not fit enough to undergo chemotherapy. However, the newer drugs also have a relevant profile of adverse effects and incur much higher costs to healthcare systems and patients."*. Given that chemotherapy is an off-label treatment this statement is not accurate albeit the fact that chemotherapy is longer established in other settings. Further,	We recommend the following wording: *"The treatment options available in mHSPC have changed substantially in recent years due to the development of novel and highly effective hormonal treatments. These treatments as well as off-label chemotherapy have a relevant profile of adverse effects and incur various costs to healthcare systems and patients, i.a., drug costs, application cost, hospitalization costs, management of adverse events costs, societal costs, etc. These have led to*	We adapted the wording of the document.

		before performing the formal analysis intended in this report, the statement on costs is premature. The treatments might have higher drug costs, but may reduce follow-on cost, hospitalization cost, reduce indirect cost and prolong life.	*controversies in other jurisdiction regarding the (off-label-) use, approval and reimbursement of these agents."*	
14	Rationale, page 5	The report states: *"The high treatment costs have led to controversies in other regulatory systems regarding the approval and reimbursement of these novel drugs (i.e., NICE for abiraterone [23])."* The NICE appraisal of abiraterone GID-TA10122 is still in development and therefore reference to NICE should be removed (https://www.nice.org.uk/guidance/indevelopment/gid-ta10122/documents).	Remove the reference to NICE	We acknowledge that the NICE appraisal is currently in development. The assessment was previously suspended (Apr 2019) due to uncertainties regarding the price at which abiraterone would be available to the NHS. We removed the reference to NICE according to your request.
15	Rationale, page 5	The report states the following: *"While oncology services commonly offer all available therapies, many patients are primarily treated by urologists, which are often less experienced in administering chemotherapy and may thus favor treatment with novel hormone therapies."* This is speculative both in terms of which patients are treated in which setting and by which specialty as well as in terms of the available treatment options.	Add reference or remove from the report.	Results from the APCCC 2019 show that physicians have varying preferences regarding the treatment of men with newly diagnosed mHSPC. We adapted the wording in the document as follows: *"Some specialists may have a preference to favor one therapy over another, which may also depend on the field of practice (e.g., medical oncology or urology)."*
16	Rationale, Objectives, or Decision	There is no characterization of the unmet need in this patient population. As this is the key driver to treatment, we believe	We would suggest adding the following paragraph to the document:	We agree that an explicit statement on the therapeutic need in the mHSPC population was missing from

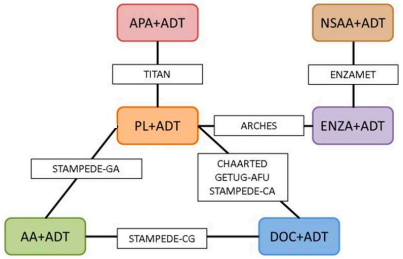
	Context (PICO)	this should be reflected in either of the suggested sections.	*“All patients with mHSPC are at risk of developing castration resistance and progressing to mCRPC. Progression to mCRPC is associated with a significant deterioration in HRQoL, as patients experience a decline in vitality and mental health, along with increased bodily pain, fatigue, loss of appetite and weight loss. Progression to mCRPC also results in an increase in tumour burden and a substantial negative impact on survival. Rising PSA levels and disease progression place a considerable emotional and social burden on patients, impacting their relationships with others and causing worry, fear, anxiety and depression, as patients anticipate developing castration resistance. mCRPC is also associated with a higher economic burden than mHSPC, as patients with mCRPC require an increased number of hospitalisations and prescriptions for outpatient drugs. Delaying the mCRPC disease stage is therefore of utmost value. The goal of treatment in mHSPC is to delay disease progression and thereby prolong survival and maintain HRQoL by delaying debilitating symptoms. Deferring treatment until disease progression occurs increases the risk*	the document. We consider the primary rationale for treatment to be prolonging the survival and improving or maintaining the quality of life of patients. Delaying disease progression is certainly also important, to the extent to which progression is associated with a decrease in quality of life or survival (i.e., is a valid surrogate for patient-relevant endpoints). We included the following statement: *"There is a therapeutic need for treating patients with mHSPC in order to prolong survival, improve or maintain quality of life, and delay disease progression."*

			of developing debilitating symptoms and leads to reduced survival."	
17	Objectives, page 5	The report states: *"The HTA aims to provide a comparative assessment of the different available systemic first-line treatments for adult men…."* Several of the studies also included treatment of mHSPC in "second line", e.g., in the TITAN study previous treatment with docetaxel was allowed and is in-label based on the EMA approval	We recommend removing the word "first-line" from the objective as a disentanglement of the different subgroups is difficult. We further would like to highlight that sequencing is therefore a question which should be considered in more details vs. the current suggestion (cf. comment above)	We acknowledge that the disentanglement of the different subgroups may be difficult and that the optimal sequencing of treatments is an important question in metastatic prostate cancer. The aim of this HTA is to determine the relative effectiveness of different treatment strategies at the time of diagnosis of mHSPC. That patients in some studies received treatments in *second line* is a known issue arising from differences in study designs. However, this HTA aims to reflect a clearly defined decision situation (i.e., *first line*) and it is important to ensure comparability of study populations when conducting NMA. Therefore, the objective has not been changed. The analysis and interpretation of the data will be conducted in accordance with data availability. We will follow clear criteria to select the most applicable data for our analysis. If helpful and appropriate, this may include data from a second line setting according to defined criteria.
18	Population, page 6	Also, here the definitions are mixed. Newly diagnosed is not per se that as	Use definitions as stated above in comment 3	Please see comment 3.

		also primary progressive patients are included.		
19	Population, page 6	The report states: *"Patients that have received chemotherapy with docetaxel prior to the start of novel hormonal therapy will be excluded"* The rationale for this exclusion is not clear and given that both TITAN and ARCHES have those subpopulations we believe they should be included	We would suggest removing this sentence and including this population in the analysis	Please see comment 17.
20	Population, page 6	As LATITUDE has a clearly defined, newly diagnosed, high risk population we believe this should be analyzed separately	Use definitions for populations as stated above in comment 3	Please see comment 3. The inclusion or exclusion of the LATITUDE study from NMA or subgroup analyses will be guided by a careful assessment of heterogeneity with respect to the other trials. Additionally, we may conduct sensitivity analyses where deemed appropriate.
21	Intervention, page 6, comparator, page 7	The report states "standard dose". This is not very precise. Cautionary note: There are some studies in Table 1 that include a broader off-label population and use of an off-label dosing schedule (James et al., 2017). Those should be reflected accordingly in the research	We would recommend changing to "licensed dose"	We adapted the wording in the document.
22	Outcomes, page 7	The report includes "*Biochemical (PSA) progression-free survival (bPFS)" as an important efficacy outcome*." In mHSPC PSA progression is not a critical outcome, as treatment should be	Remove this outcome from the list of efficacy outcomes	We aim to include the PFS outcome from each trial, which most closely reflects a meaningful clinical progression (either by leading to a decrease in quality of life, or to a change in treatment). Out of the listed

		continued until radiographic or clinical progression as per studies and indications.		outcomes (clinical PFS, radiographic PFS, failure-free survival and biochemical PFS), bPFS is considered to be least patient-relevant. We will only use bPFS data from a study if no other PFS outcome is available. We changed the wording of the PFS outcome, so that it reflects our *a priori* prioritization for evidence selection.
23	Outcomes, page 7	Progression to subsequent treatments (PFS2) is a crucial outcome for patients. We therefore believe inclusion of this outcome adds to the value of the report	Add the following outcome: • Second progression free survival (PFS2)	Please see comment 11.
24	Subgroups of interest, page 8		In line with above comments we would suggest the additions of the following subgroups: • Prior chemotherapy exposure vs. not • Visceral metastasis vs. not	Please see comment 17. As this HTA is primarily focused on *first line* treatments in mHSPC, patients with prior chemotherapy exposure are not primarily considered eligible. Data from patients with prior chemotherapy exposure may only be used if no more applicable subgroup data is available and effect modification is deemed implausible. It is unclear to us from the comment why "visceral metastasis vs. not" should be considered in a subgroup analysis. In the scoping, we did not encounter strong arguments in support of such a subgroup analysis. We have currently left the prespecified subgroup analyses unchanged. If the need arises,

				additional subgroup analyses can be added but will be denoted as not pre-planned.
25	Subgroups of interest, page 8	The report plans to do a subgroup analysis on high vs. low volume disease	Recent data from the STAMPEDE trial called the relevance of high vs. low volume into question. Therefore, we would suggest removing this subgroup analysis	Please see comment 3.
26	Data analysis and synthesis, page 10	Subsequent, life prolonging therapies might significantly impact OS.	Consider/Discuss the impact of subsequent therapies on OS	Subsequent treatments after progression are an important issue to consider when interpreting data from studies in mHSPC. This topic will be discussed in the HTA. We added the following statement to the section on Data Analysis and Synthesis: *"Furthermore, we will analyze and discuss the impact of subsequent treatments after progression (i.e., treatment sequencing) on the results."*
27	Data analysis and synthesis, page 11, figure 1	• The populations of STAMPEDE and LATITUDE do not match and should therefore be handled separately The ENZAMET and ARCHES study have different interventions and are not connected through ADT. The assumption that ADT + nsAA performs the same as ADT alone is not validated in literature	• The LATITUDE population should be a separate population and only looked at in a subgroup analysis to avoid introduction of bias • ENZAMET should be a separate arm on its own which is linked to the network only through ADT + enzalutamide	Please see comment 20. We made the decision to use ADT±nsAA after a detailed consideration of the evidence. Unfortunately, the literature is currently insufficient to judge whether effects of ADT and ADT+nsAA (or combined androgen blockade) are different in mHSPC. To our knowledge, no recent high-quality meta-analyses are available in this context, and most potentially relevant trials were conducted before *newly*

			We would suggest the following network:  	*diagnosed mHSPC* emerged as a distinct diagnostic entity, potentially affecting the comparability of trials. This approach has also been followed by other authors (e.g. Di Nunno 2020, Salathianen 2019, Marchioni 2019). The potential impact of this choice will be discussed in the HTA, and the separation of ADT and ADT+nsAA arms may be considered in a sensitivity analysis.
28	Data analysis and synthesis, page 11, figure 1	Inclusion of ENZAMET study in the network.	Cautionary note: The ENZAMET trial had a very specific design, significantly different to the other trials, limiting the information it provides, i.e., open label, non-SoC comparator arm of CAB+ADT, co-administration of chemotherapy in a subgroup, lower statistical power, no European enrollment	This is an important remark. We will evaluate the appropriateness of including the ENZAMET trial in the network after a detailed analysis of the extracted data. We may conduct sensitivity analyses with respect to data from this trial, if deemed appropriate.
29	Data analysis and synthesis, page 11		Given the significant challenges with the comparability of the different studies and the limited amount of information provided in the scoping document we would like to invite the researches to perform an additional stakeholder engagement round after the draft finalization of the statistical analysis plan to ensure that the known pitfalls are addressed accurately	We highly appreciate the offer of an additional stakeholder feedback round. However, conducting another stakeholder engagement at the current stage would lead to a significant delay in the conduct of the HTA. Given our experience with evidence synthesis and network meta-analysis, economic evaluation and HTA, we are confident to make appropriate assumptions and judgements in the individual parts of this HTA. If further input or insights

				from experts or industry are needed, we will be happy to directly contact the respective stakeholders.
30	Brief overview of the identified cost-effectiveness analyses, page 12	It is unclear how the CE values (in CHF) were calculated for Table 2 and which assumptions were made	Show calculations and assumptions	The calculations of the cost-effectiveness estimates were conducted by the respective authors of the publications, which may incorporate various assumptions. Please refer to the original publications for greater detail. We converted the estimates into CHF using respective exchange rates to provide a rough overview of the economic evidence. In the economic analysis, the available publications will be analyzed in greater detail and refined approaches to conversions will be used. No changes were made to the scoping document.
31	Cost-effectiveness analysis, page 14	The current level of detail provided is limited and does not allow to assess the suitability of the chosen approach	Perform an additional round of stakeholder feedback, once the uncertainties around the approach are clarified	Please see comment 29.
32	Budget impact analysis, page 15	The current draft seems to focus solely on the consequences in mHSPC, however, offsetting cost in subsequent populations has a significant impact on overall healthcare cost and must be considered when assessing the consequences in mHSPC	Cost of subsequent treatments are a crucial part of budget impact and should therefore be considered as well	It is clear that subsequent treatments and associated costs should be considered when evaluating treatments for mHSPC. We will incorporate such information and assess the underlying assumptions to the extent feasible given the available data.

33	Benefit harm Assessment, page 16	The report states the following: *"However, only little experience is currently available about appropriate methodological approaches in this area"* Based on the above it seems that the researcher would like to focus on method development and gain experience with the suggested method.	Given the ambitious goals of the project with impact on actual treatments in Switzerland and also on the market authorization and reimbursement processes stated by the authors it seems premature to include a method which has not been sufficiently developed. We would therefore advise to perform this analysis (if desired) separately and independently of the current HTA. We would rather encourage the full inclusion of the patient preference study as this one has a more direct impact on patients' needs	While we agree that more experience is needed with the conduct of BHA in the context of cancer drugs, we do not agree with the reasoning that such research should not be conducted due to methodological uncertainties. Quantitative BHA is a systematic and transparent approach that allows to incorporate and explore uncertainties and to conduct a wide range of sensitivity analyses regarding the underlying data and model structure. Furthermore, BHAs are commonly conducted by the FDA and EMA for drug approval processes and it has become clear that BHA should be an integral part of HTA. For more detail on the rationale for conducting a BHA, please refer to the supplement to the scoping document (dated 17 Dec 2019). We consider BHA an essential component for this HTA, which will add an important dimension to the evaluation of mHSPC treatments. Meanwhile, the weight given to the findings of the BHA in the appraisal process remains flexible and is at the discretion of the appraisal committee. It has been decided that the preference study will not be funded by the Swiss Medical Board and may be conducted as an independent project under separate funding.

34	Expected impact and public health relevance, page 18	The report states the following: *"The findings of this HTA may be highly relevant for upcoming regulatory decisions in Switzerland when it comes to the market authorization of novel hormonal therapies in mHSPC".* Market authorization is a process where the benefits and risks of a technology are assessed based on the submitted clinical trials. It is unclear, how this analysis should impact the market authorization of products under the current legislation	This sentence should be removed or adjusted to reflect the current legislation	Under the current legislation, market authorization and reimbursement/ pricing negotiations in Switzerland are indeed in the competency of swissmedic and the Federal Office of Public Health. As such, the findings of this HTA will not have a direct influence on upcoming decisions or negotiations. We apologize for the misleading wording, which we have adapted in the document as follows: "*The findings of this HTA will provide complementary evidence that may be highly relevant in light of upcoming regulatory and reimbursement decisions on novel and established treatments for mHSPC in Switzerland, as well as future pricing negotiations in this context*."
35	Expected impact and public health relevance, page 18	The report states the following: *"In addition, our results may also support pricing negotiations for novel cancer drugs, drugs with an extension of indication, or potentially even future generic versions of currently patented drugs in this context."* The current legislation regarding price finding in Switzerland consists of TQV/APV and innovation bonus. HTA as such does not have a formal place in price negotiations, especially given the lack of a formal ICER in Switzerland. Further the suggested approach is only	Remove this sentence or adjust to reflect the limitations given the current Swiss legislation	Please see comment 34.

		one of the potential health economic approaches and hence other factors must be considered as well.		
36	Timelines & Milestones, page 19	There are several mentioning of “stakeholders”. Those are not made transparent and therefore do not allow the reader to make an adequate judgement of the process	Clarify, who is a stakeholder and at what timepoint they were involved in which fashion, including experts listed in the beginning. Further, conflict of interests of experts and involved scientists should be stated	Please see comment 1. A detailed stakeholder list will be compiled and provided with the HTA report.

Due to a technical communication issue, the stakeholder feedback from Janssen-Cilag AG was received after the start of the project and was incorporated in a revised scoping document (v3.0, 13 Mar 2020). Compared to the previous version of this document (15 Nov 2019), this document additionally includes the feedback by Janssen-Cilag AG and the respective point-by-point responses by the assessment team. No changes were made to the rest of the document.