

INTRODUCING ETHICON'S BARBED MONOCRYL AND PDS DEVICE: STRATAFIX™

Why Knot?



If you can use

Stratafix™

A SUTURE FOR TODAY'S EVOLVING SURGICAL LANDSCAPE

TO LEARN MORE ABOUT STRATAFIX:

[BOOK A VIRTUAL CONSULT HERE](#)

ETHICON | Shaping
the future
of surgery
PART OF THE Johnson & Johnson FAMILY OF COMPANIES

For complete indications, instructions for use, contraindications, warnings, precautions, and adverse reactions, please reference full package insert.
Colouring of product image depicted for illustrative/marketing purposes only and may differ from actual product. Johnson & Johnson Medical Pty Ltd, 15
Khartoum Road, North Ryde, NSW 2113. 208073-220329, March 2022

Expert consensus on novel medicines to prevent preterm birth and manage preterm labour: target product profiles

Annie RA McDougall^{1*}, Andrew Tuttle², Maya Goldstein², Anne Ammerdorffer³, Lily Aboud¹, A. Metin Gülmezoglu³ & Joshua P. Vogel^{1,4}.

1. Maternal, Child and Adolescent Health Program, Burnet Institute, Melbourne, Australia
2. Policy Cures Research, Sydney, Australia
3. Concept Foundation, Geneva, Switzerland
4. School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

*Corresponding author:

Dr Annie McDougall
Maternal, Child and Adolescent Health Program,
Burnet Institute,
Melbourne, Australia
Email: annie.mcdougall@burnet.edu.au
Phone: +61-3-9282-2111

Short title: Target product profiles: preterm birth medicines

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/1471-0528.17314](https://doi.org/10.1111/1471-0528.17314)

ABSTRACT

Objective: To develop target product profiles (TPPs) for new medicines for preterm birth prevention and preterm labour management that address the real world need of women and health care providers, informed by views and agreement amongst globally diverse stakeholders.

Design: Mixed-methods.

Setting: Global (focus on low and middle-income countries (LMICs)).

Population or sample: Global stakeholders with diverse expertise in preterm labour/birth and drug development.

Methods: Following an initial literature review, diverse stakeholders were invited to participate in an online international survey and in-depth interviews. The level of stakeholder agreement with TPPs was assessed, and findings from interviews were synthesised to inform the final TPPs.

Main Outcomes Measures: Level of stakeholder agreement on the minimum and preferred requirements for preterm labour/birth medicines.

Results: We performed 21 interviews. Interview participants demonstrated strong agreement on room temperature stability, no additional drug-specific clinical monitoring, and affordability in LMICs being minimal acceptable requirements. Points of discussion were raised around the target population. Survey respondents included clinicians, researchers, funding agency staff, international public organisation staff, programme implementers, policymakers, representatives of consumer advocacy organisations and other relevant maternal health systems stakeholders. Survey results indicated strong agreement amongst stakeholders, with only one variable in each TPP not reaching consensus (25% disagree or strongly disagree).

Conclusion: There is strong consensus within the preterm labour/birth community on characteristics that new medicines for preterm birth prevention and preterm labour management must achieve. These TPPs provide necessary guidance to evaluate new candidates and their potential for implementation in a range of settings.

Keywords: TPPs, tocolytics, maternal medicines, obstetric medicines, spontaneous preterm birth, PPRM, global health

Tweetable abstract (110 characters): Consensus-driven target product profiles for new medicines to prevent preterm birth and manage preterm labour.

INTRODUCTION

Preterm birth (birth before 37 completed weeks of gestation) is the leading cause of death in children under 5 globally; 35% of neonatal deaths are caused by complications of preterm birth.(1) Nearly 15 million babies are born preterm annually, ~80% of which occur in Africa and South Asia, much of which are limited-resource settings.(2) Preterm babies are at increased risk of short- and long-term adverse health outcomes, including chronic lung disease, infections, and neurological, visual and auditory disabilities.(3, 4) Up to 50% of preterm births are due to spontaneous preterm labour, with an additional 25-30% due to preterm pre-labour rupture of membranes (PPROM).(5) The aetiology of spontaneous preterm birth, while not well understood, is multifactorial, and can involve infection, inflammation, uteroplacental ischemia or haemorrhage, uterine overdistension or stress.(6)

Currently, there are very few effective medicines recommended for the prevention of preterm birth.(7) Effective preventive agents are available for women with specific risk factors, such as progesterone for women with previous preterm birth and/or short cervix.(8) In women experiencing spontaneous preterm labour, tocolytic agents can slow or stop contractions, providing time to administer corticosteroids for fetal lung maturation or allow transport of women to higher-level health facilities.(9) Several tocolytic agents are used internationally, including calcium channel blockers, betamimetics, nitric-oxide donors, COX-inhibitors, magnesium sulfate and oxytocin receptor antagonists, which likely prolong pregnancy for 2 to 7 days and some of which may improve newborn health outcomes.(10)

Despite 2.4 million neonatal deaths, 2 million stillbirths and 295,000 maternal deaths occurring globally each year,(11-13) drug development for pregnancy-related conditions remains severely underfunded and inadequate.(14) In 2020, the Accelerating Innovation for Mothers (AIM) project was created with the goal of invigorating investment in research and development (R&D) to address the “drug drought” in medicines for pregnancy-specific conditions. AIM is a collaboration between Concept Foundation, Policy Cures Research and Burnet Institute, which envisions a world where medicines

and technologies are developed and made accessible to women for pregnancy-specific conditions. Across all AIM activities, data has been collected from over 20 countries.

Target product profiles (TPPs) are a well-recognised strategy to promote development of innovative medical products, such as devices, diagnostic tests, and therapeutics (15-17) and are an important resource for multiple stakeholders in the R&D pathway, including funders, researchers, product developers, manufacturers and regulators.(17) TPPs are a document that specifies the minimum and preferred characteristics that a new product should take, to fulfil a clinical need. TPPs can also be used to identify, prioritise and evaluate new candidate products. Developing a TPP is a consensus-generating process, requiring input from diverse key stakeholders to align around a clear set of product goals and characteristics.(15)

TPPs have been used to address numerous public health gaps, including new vaccines, antibiotics, HIV cures and infectious disease diagnostics.(15, 18-21) However, a review of the literature and WHO Health Product Profile Directory revealed that there are no publicly available TPPs for medicines for maternal conditions, including preterm birth. WHO and UNICEF have developed TPPs for neonatology, including for antibacterial agents for neonatal sepsis and devices used for newborn care.(21, 22) As part of the AIM project, we developed two new TPPs for medicines to prevent and treat pre-eclampsia.(23) In this study, we used quantitative and qualitative methods to develop new TPPs describing medicines for prevention of preterm birth and management of preterm labour.

METHODS

We prepared a study protocol on TPP development informed by methods used in recent TPPs for HIV cures and diagnostic tests for sexually transmitted infections, and adopted the five-step process used by Lewin et al (Figure 1).(15, 18, 19, 24) The protocol was approved by the Alfred Ethics Committee for Human Research (project number 108/21), and informed consent was obtained from all participants prior to their participation.

Step 1: Initial drafting phase

On the 9th March 2021, the AIM project convened a multi-disciplinary advisory group of 11 experts from diverse backgrounds (drug development research, maternity clinical practice, consumer advocacy, maternity health program implementation, social enterprise, funders, and international agencies) with diversity in gender and geographical location. In consultation with this advisory group, preterm birth was selected for the development of two TPPs for 1) agents for preventing preterm birth in women at increased risk; and 2) agents for the management of preterm labour (tocolysis; Figure 1).

Initially, we sought to define the intended use-case scenario for prophylactic medicines for preterm birth and therapeutic medicines for preterm labour, the key variables for the TPPs, and the acceptable minimum and preferred targets for each of these variables. Through literature review and AIM team consultations, intended use-case scenarios were developed, which were revised in subsequent phases (Box 1 presents the final versions). Given the considerable burden of preterm birth affecting women in low- and middle-income countries (LMICs), we specified that a primary focus of the TPPs were to drive development of medicines that could be used safely and effectively for women living in limited-resource settings. We collated TPP templates and guidance produced by several reputable organizations (USFDA, Bill & Melinda Gates Foundation, WHO, PATH and others) and developed a TPP template with 21 domains. Through literature reviews we developed draft minimum and preferred targets for each domain, along with additional annotations including the rationale and supporting evidence (original draft TPPs available as supplemental data 1 and 2).

Step 2: International stakeholder survey

We conducted an international online stakeholder survey to seek participants input on use-case scenarios and minimum and preferred targets for each variable. We used the survey approach of Pelle et al in their development of TPPs for clinical decision support tools(19) using Qualtrics (Provo, USA), and pre-tested it on two individuals prior to launch. Respondents were asked to rate their agreement with the minimum and preferred targets for each domain using a Likert scale (1 equals strongly disagree and 5 equals strongly agree). Optional comments were invited for each domain.

Professionals working in the field of maternal and perinatal health (including clinicians, researchers, funding agency staff, international public organisation staff, programme implementers, policymakers, representatives of consumer advocacy organisations and other relevant maternal health systems stakeholders) were invited to participate in the survey. We sought diverse representation from participants in high-, middle- and low-income countries. In total, 273 individuals were invited to participate using the following databases: 1) AIM project database of relevant maternal health R&D experts; 2) a database of all individuals who had participated in WHO maternal and perinatal health guideline development groups in the past 12 years;(25) and 3) members of the WHO Multi-Country Survey on Maternal and Newborn Health research network.(26) In addition, the survey was distributed through other clinician-researcher networks and listservs, including the Cochrane Pregnancy and Childbirth network and the Perinatal Society of Australia and New Zealand, as such we cannot calculate an exact response rate. We pre-specified a minimum of 50 responses per domain to evaluate the degree of consensus. We defined agreement as $\geq 75\%$ of respondents selecting agree or strongly agree for a specific variable. The survey was active for 31 days (Figure 1). Demographics of the final survey respondents are presented in the results.

Step 3: Stakeholder interview phase

In parallel with the online survey, we conducted in-depth, one-on-one interviews with stakeholders with a particular interest in preterm birth, maternal health drug development and implementation. The goal of these interviews was to seek more detailed feedback on the use-case scenarios and requirements for each variable. Stakeholders were identified from the same databases used for the survey. In addition to appropriate expertise on the topic of interest, diversity of gender, geographical location and technical expertise was sought (Figure 1). Interview participants were not identified from the survey participants.

Stakeholders were initially invited to participate via email and were provided drafts of the TPPs to read prior to the interviews. Interviews were conducted over Zoom by an AIM project researcher, using a semi-structured, pre-tested interview guide. Informed consent was obtained before the interview began and each interview lasted approximately 60 to 90 minutes. Interviews were conducted in English. The interview

guide involved discussing the TPP variables sequentially, with particular emphasis on variables relevant to their area of expertise or interest. We explicitly sought participants views on applicability across different countries and resource levels. Participant responses were captured via interview recordings and field notes. Interview recordings were only referred to if field notes were unclear on a particular variable.

Step 4: Public consultation

The draft TPPs were made available online for public comment via the Burnet Institute and Concept Foundation websites. The consultation period lasted approximately four weeks (concurrent with the international online survey) and was disseminated via social media (Figure 1).

Step 5: Synthesis and finalisation

The results of the international online survey were analysed, and those domains where consensus was not reached were identified. Consensus was defined as 75% or more of respondents who agreed or strongly agreed with the minimum and preferred criteria. The outputs of expert interviews were summarised, with key themes and “major” or “minor” concerns identified. Variables where consensus was not achieved, or where strong disagreement was identified via interviews, were modified based on stakeholder feedback. The final drafts were shared with the AIM expert advisory group for comments before finalisation and publication (Figure 1).

RESULTS

Survey and public consultation results

We received 46 responses to the survey. Respondents were from across all WHO geographical regions (Figure 2A). Participants represented diverse expertise, selecting the best description of their current role as clinicians (doctor, midwife or nurse, 39.1%), researchers (37.0%), epidemiologists (4.3%), staff of not-for-profit organisations (6.5%), staff of international public organisations (2.2%), staff of health programmes (4.3%), staff of funding agencies (2.2%) and other (including participants who identified as more than one option, 4.3%).

Survey results showed high agreement (consensus; $\geq 75\%$) across almost all variables of both TPPs (Figure 3). For preterm birth prevention, agreement was less than 75%

for the minimum requirements regarding the acceptable level of adherence to the medicine regimen (20% of respondents disagreed or strongly disagreed; Figure 3A). For treatment of preterm labour, agreement was less than 75% for the preferred requirements regarding the WHO pre-qualification of the medicines (29% neutral, 0% disagree or strongly disagree; Figure 3D). Consensus was achieved for all other variables in both TPPs. No comments were received via the public consultation website.

Findings from stakeholder interviews

A total of 40 stakeholders were invited to participate in an interview, of which 21 stakeholders (13 females and eight males) responded; all interviews were conducted between August and October 2021. Like the survey respondents, the interview participants represented diverse gender, geographical and expertise. Participants were from Africa, Asia/Pacific, Europe, USA and South and Central America (Figure 2) and included nine obstetrician/researchers, two drug development experts, two consumer representatives, two midwives, two neonatologists, two maternal medicines procurement experts, one basic scientist, one programmes implementation expert, and one WHO staff member. Compared to survey respondents, there was a slightly higher proportion of interview participants from the Western Pacific region, and a slightly lower proportion from the African region. There were no interview participants from the Eastern Mediterranean region, although they were represented in the survey.

Although survey respondents strongly agreed with the target population for both preterm birth prevention (*Minimum: 89%; Preferred: 92%*) and preterm labour management (*Minimum: 88%; Preferred: 88%*), several interviewees disagreed with the definition of the target population in both TPPs. Numerous interviewees raised concerns with the broad definition of the target population for the prevention of preterm birth and felt that a more precise definition was required. Specifically, there was confusion as to whether all forms of preterm birth (i.e., spontaneous, PPRM and provider-initiated) were being targeted and whether one drug would be able to prevent preterm birth in all these situations.

In the TPP for medicines to treat preterm labour, many interviewees did not agree with the proposed target population of women <34 weeks' gestation in spontaneous

Accepted Article

preterm labour. The initial draft of the TPP used <34 weeks' gestation due to WHO's 2015 recommendation that women at risk of imminent preterm birth be treated with antenatal corticosteroids (ACS) for fetal lung maturation in this situation.⁽⁹⁾ However, interviewees suggested that women <37 weeks' gestation would be a more appropriate target population, considering that: tocolytics can be useful after 34 weeks' gestation to support transport of women in spontaneous preterm labour to a higher level of care; that in many low-resource settings it is not possible to determine with confidence a woman's gestational age; and that in some settings women at risk of preterm birth at 34 to <37 weeks' gestation are given ACS.^(9, 27-29) Some interviewees also suggested that the minimum acceptable level of treatment adherence (i.e. a tolerable discontinuation rate of <35%) was too high, which was reflected in a high level of disagreement on this variable in the survey. One interviewee remarked that any preventive medicine with a discontinuation rate greater than 20% would be unlikely to have meaningful public health impact.

There was strong agreement among all interviewees that new medicines should not require cold-chain transport or storage, that any new medicines should not require additional clinical monitoring of mother or baby, and that medicines should be affordable in LMICs. These findings were reflected in the survey results. All but two interviewees strongly agreed that any new medicine should not require the use of a companion diagnostic test as a requirement for its routine use. Two interviewees suggested that the use of a companion diagnostic test for bacterial vaginosis could be beneficial to targeting the use of preventive agents but agreed that such a requirement may limit widespread implementation in limited-resource settings.

The question of whether evidence of improvement to perinatal health outcomes should be included as a minimum (rather than a preferred) requirement in both TPPs was raised by numerous interviewees. Some felt that in order for any new agent to be used widely, demonstration of improved perinatal outcomes (i.e., reduced neonatal mortality) was essential. However, other interviewees felt that it was acceptable as a preferred requirement, given the difficulty in conducting large trials that could demonstrate benefits. These interviewees considered evidence of reduced incidence of preterm birth (prevention TPP) and evidence of a clinically important difference in

extending pregnancy duration (treatment TPP) were themselves compelling evidence of benefit and were thus appropriate as a minimum requirement.

Although the survey showed a high level of agreement for the safety requirements in both TPPs, a small number of interviewees disagreed with the inclusion of lactating women, suggesting that this was not relevant as these medicines would not be used postpartum. However, many interviewees felt that lactating women should be specified, as medicines with a long half-life may have implications for breastfeeding immediately after birth. Several participants felt that protecting breastfeeding was particularly critical for women living in LMICs, due to the considerable barriers associated with formula feeding, such as cost and access. One interviewee with experience as a health care professional in LMICs stated pregnant women may also be breastfeeding other infants while pregnant. Another minor issue identified by some interviewees was that in both TPPs, vaginal administration should be included as a non-invasive administration route.

Finalisation of TPPs

Following the synthesis of findings from the survey and the stakeholder interviews, the authors refined the target population definition in both TPPs (Table S1 and S2). For medicines to prevent preterm birth, the target population in the TPP specifies “women with identified risk factors for spontaneous preterm labour” only (Table S1). For medicines to treat preterm labour, the upper gestational age limit of the target population in the TPP is <37 completed weeks’ gestation (Table S2). In the TPP for prevention of preterm birth, the minimum treatment adherence was changed to <30% discontinuation (Table S1). Vaginal administration was also included within the Formulation, Dosage and Administration variables in both TPPs. Improving neonatal outcomes remained as part of the preferred requirement for clinical efficacy, and “not contraindicated in lactating women” remained a minimum safety requirement in both TPPs (Table S1 and S2).

DISCUSSION

Main findings

Using multiple methods, including quantitative surveys and qualitative in-depth interviews with diverse experts, we have conducted the first study to comprehensively evaluate the requirements for new maternal medicines to prevent preterm birth and manage preterm labour. Our findings highlight that across multiple stakeholder groups (including basic research, obstetrics, midwifery, neonatology, drug development, maternal medicines procurement, programmes implementation, WHO and consumer advocacy) there was strong agreement on the characteristics that new medicines for preterm birth and labour must take to meet the real-world needs of women and providers. There was agreement from surveys and interviews that for any novel or repurposed medicine: 1) cold-chain transport and storage should not be required; 2) that any medicine should require minimal to no additional drug-specific clinical monitoring of mother or baby; 3) non-invasive administration routes such as oral medicines are preferred; and 4) medicines would need to be affordable in LMICs.

In this study, the variables that provoked the highest level of disagreement or discussion were about the target population for both TPPs. Additional areas of discussion included the importance of safety during breastfeeding of any new medicines and the benefits versus implementation barrier of a required clinical diagnosis for use of medicines.

Interpretation (in light of other evidence)

Development of new obstetric medicines - including those for preterm birth prevention and management - is under resourced and poorly coordinated.⁽³⁰⁾ Mapping of maternal research funding demonstrates that very few donors place a high priority on maternal health intervention studies.⁽³¹⁾ This is particularly true for the pharmaceutical industry – a 2014 analysis by Footman *et al* assessed 2340 studies on maternal health interventions in LMICs, reporting that pharmaceutical companies were involved in only 7% of these studies.⁽³¹⁾ There is a clear market failure in the R&D for new maternal medicines. As of 2008, there were fewer drugs in active development for all maternal conditions than for the rare disease amyotrophic lateral sclerosis.⁽¹⁴⁾ The “drug drought” in maternal medicines has led to only two new drugs, the tocolytic atosiban and carbetocin for prevention of PPH, being licenced specifically for use in pregnant women in the last 30 years.⁽³²⁾ Unlike the global efforts for HIV and malaria treatments, there has been no global systematic effort to improve maternal medicine

R&D and identify candidate medicines that meet the real-world needs of women and providers, particularly for those living in LMICs where newborn and maternal morbidity and mortality are unacceptably high.(11, 31, 33) TPPs developed by WHO for other areas of reproductive health – such as sexually transmitted infection diagnostics - are highly valued by R&D companies, who are using them to guide the development of new tests.(34) TPPs describing new medicines for obstetric conditions have not been prioritized prior to the AIM project but are now being identified as a tool to promote innovative advances for women. In addition to the two TPPs we have developed for pre-eclampsia medicines,(23) researchers at the University of Birmingham are also developing a TPP for endometrial receptivity tests for recurrent miscarriage.(35) The TPPs developed during this study will provide guidance to prioritize research towards candidate medicines that best meet the needs of women at risk of or experiencing preterm birth.

Underfunding and siloed research means there are very few medicines available for women at risk of preterm birth or in preterm labour. Currently, calcium channel blockers, betamimetics, nitric-oxide donors, COX-inhibitors, magnesium sulfate and oxytocin receptor antagonists are used for tocolysis, though there is only low to very low GRADE evidence that these tocolytics themselves improve substantive perinatal outcomes outcomes.(10) Atosiban, an injectable oxytocin antagonist that requires cold chain, is the only recommended drug specifically developed as a tocolytic and is only available in some high income settings, and not in USA. All other medicines are repurposed tocolytics and have undesirable safety profiles (e.g. betamimetics) or accessibility challenges (e.g. nifedipine).(10, 36) Noting the lack of evidence of benefits for tocolytic agents, WHO's 2015 guidelines recommend against tocolysis for women in spontaneous preterm labour,(9) although they are currently under review. However, they do specify that oral nifedipine can be considered in order to provide a treatment window for administration of antenatal corticosteroids and/or transport to an appropriate care setting.(9) Nitric oxide donors such as nifedipine are the highest ranked tocolytic for delaying preterm birth,(10) and oral nifedipine meets many of the variables specified in the current TPP, including no need for cold-chain, non-invasive administration and minimal additional monitoring of the mother. Many national guidelines recommend the use of tocolytics for women in preterm labour to delay birth by 48 hours, but the choice of tocolytic differs between guidelines.(37) Some studies

have reported that obstetric care providers are unsure about the appropriate use of tocolytics, and have identified significant differences between guideline recommendations and actual clinical practices.(38-40) We therefore believe that these TPPs will be helpful to guide the development of new products that are needed.

There are few options for medicines to prevent preterm birth. Evidence for the use of progesterone in women at risk of preterm birth (history of preterm birth and/or cervical shortening) is increasing(8) and some national and international guidelines recommend its use for the prevention of preterm birth.(41-43) Progesterone meets many of the criteria within the current TPP such as no cold-chain requirements and non-invasive administration, however, questions remain about the most effective administration and formulation of progesterone, and the indications for use (such as short cervical length, which requires performance of an ultrasound) may not be easy to identify in all settings.(8) In addition, the USFDA proposed that Makena (hydroxyprogesterone caproate injection) be withdrawn from market due to evidence of a lack of clinical benefit in preventing preterm birth.(44) From a clinical perspective, new medicines for both the prevention of preterm birth and management of preterm labour are needed.

This study has identified strong agreement from diverse stakeholders, on the requirements new preterm birth medicines should meet. TPPs, such as those developed from this research, provide guidance to involved stakeholders, researchers and companies that can help drive development of candidates that are most likely to meet real-world needs. For funders, these TPPs can be used to set targets for R&D and promote research investment in the most promising candidates that meet or mostly meet the parameters defined in this study. TPPs are also a tool that allow regulatory agencies to evaluate new candidates and their potential for implementation in a range of settings. Prioritising R&D funding for candidate medicines that meet or mostly meet the requirements of the TPPs can drive development of medicines that will address the needs of women and providers, particularly in LMICs.

Strengths and limitations

We have described the development of the first TPPs for medicines to prevent preterm birth and manage preterm labour. Given the global diversity of expertise of

Accepted Article

participating stakeholders, the results of this study can be considered a reflection of the needs of women, healthcare providers, researchers and drug developers, and will facilitate the development of new medicines for preterm birth that can be globally implemented. One limitation was that we performed only one round of the international survey to identify levels of agreement. In other TPP development activities (e.g.: for HIV cures) high levels of disagreement for some TPP variables necessitated a second survey round with stakeholders to reach consensus.(15) However, in this study we reached consensus across nearly all variables in a single round. Though the exact response rate of the survey cannot be determined (as it was disseminated through multiple channels and listservs), a larger number of responses may have yielded different levels of agreement, however given the high level of agreement we believe this to be unlikely. Another limitation is that we were unable to define a specific target affordable price that new medicines should meet, which is often included in TPPs.(24) However, given the variety of preterm medicines currently being evaluated,(45, 46) as well as the different pricing structures used across global markets, we considered that defining a specific target price would be inappropriate.(24) In future updates of the TPPs, and as more specific target medicines are identified, economic analyses could be incorporated as a key variable in these TPPs.

Conclusions

Without strategic guidance, there is unlikely to be any major advances in maternal medicines for preterm birth. We have identified strong agreement within the preterm birth community on the requirements of new medicines to prevent preterm birth and manage preterm labour. These TPPs can be used to align and streamline the efforts of funders, researchers, clinicians, pharmaceutical companies and other product developers on products that will meet the real-world needs of pregnant women and preterm newborns.

Acknowledgements: The authors would like to thank the expert advisory committee to AIM(23) and the stakeholders who participated in this study.

Competing interests: We declare no competing interests.

Funding: This project was funded by the Bill and Melinda Gates Foundation.

Details of Ethics Approval: The protocol was approved by the Alfred Ethics Committee for Human Research (project number 108/21), and informed consent was obtained from all participants prior to their participation.

Data availability: All data relevant to the study are included in the article or uploaded as supplementary information.

Author contributions: JPV and AMG led the conceptualisation and supervision of the project and funding acquisition. AMcD, AT and MG were involved in conceptualisation of the project and development of the methodology. AA was involved in conceptualisation of the project, funding acquisition and project administration. AMcD and LA performed collection, management, visualisation and analysis of all data. All authors were involved in interpretation of data. AMcD wrote the original draft of the manuscript and all authors contributed to writing and editing and had full access to the data. AMcD and JPV has accessed and verified all the data in this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

REFERENCES

1. Wardlaw T, You D, Hug L, Amouzou A, Newby H. UNICEF Report: enormous progress in child survival but greater focus on newborns urgently needed. *Reprod Health*. 2014;11:82.
2. Chawanpaiboon S, Vogel JP, Moller AB, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health*. 2019;7(1):e37-e46.
3. Cheong JL, Doyle LW, Burnett AC, Lee KJ, Walsh JM, Potter CR, et al. Association Between Moderate and Late Preterm Birth and Neurodevelopment and Social-Emotional Development at Age 2 Years. *JAMA Pediatr*. 2017;171(4):e164805.
4. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in Care Practices, Morbidity, and Mortality of Extremely Preterm Neonates, 1993-2012. *Jama*. 2015;314(10):1039-51.
5. Morisaki N, Togoobaatar G, Vogel JP, Souza JP, Rowland Hogue CJ, Jayaratne K, et al. Risk factors for spontaneous and provider-initiated preterm delivery in high and low Human Development Index countries: a secondary analysis of the World Health Organization Multicountry Survey on Maternal and Newborn Health. *BJOG : an international journal of obstetrics and gynaecology*. 2014;121 Suppl 1:101-9.
6. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet*. 2008;371(9606):75-84.
7. Care A, Nevitt SJ, Medley N, Donegan S, Good L, Hampson L, et al. Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis. *Bmj*. 2022;376:e064547.
8. Group E. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. *Lancet*. 2021;397(10280):1183-94.
9. WHO recommendations on interventions to improve preterm birth outcomes. Geneva: Switzerland; 2015.
10. Wilson A, Hodgetts-Morton VA, Marson EJ, Markland AD, Larkai E, Papadopoulou A, et al. Tocolytics for delaying preterm birth: a network meta-analysis (0924). *Cochrane Database Syst Rev*. 2022;8:CD014978.
11. WHO, UNICEF, UNFPA, Group WB, UN. Trends in maternal mortality 2000 to 2017: estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division. Geneva: WHO; 2019.
12. Hug L, You D, Blencowe H, Mishra A, Wang Z, Fix MJ, et al. Global, regional, and national estimates and trends in stillbirths from 2000 to 2019: a systematic assessment. *Lancet*. 2021;398(10302):772-85.
13. WHO. Newborn mortality Geneva; Switzerland2022 [Available from: <https://www.who.int/news-room/fact-sheets/detail/levels-and-trends-in-child-mortality-report-2021>].
14. Fisk NM, Atun R. Market failure and the poverty of new drugs in maternal health. *PLoS Med*. 2008;5(1):e22.
15. Lewin SR, Attoye T, Bansbach C, Doehle B, Dube K, Dybul M, et al. Multi-stakeholder consensus on a target product profile for an HIV cure. *Lancet HIV*. 2021;8(1):e42-e50.
16. Kadam R, White W, Banks N, Katz Z, Dittrich S, Kelly-Cirino C. Target Product Profile for a mobile app to read rapid diagnostic tests to strengthen infectious disease surveillance. *PLoS One*. 2020;15(1):e0228311.

17. Food and Drug Administration. Guidance for Industry and Review Staff Target Product Profile — A Strategic Development Process Tool (Draft Guidance). 2007.
18. Ferreyra C, Osborn J, Moussy F, Alirol E, Lahra M, Whiley D, et al. Developing target product profiles for *Neisseria gonorrhoeae* diagnostics in the context of antimicrobial resistance: An expert consensus. *PLoS One*. 2020;15(9):e0237424.
19. Pelle KG, Rambaud-Althaus C, D'Acremont V, Moran G, Sampath R, Katz Z, et al. Electronic clinical decision support algorithms incorporating point-of-care diagnostic tests in low-resource settings: a target product profile. *BMJ Glob Health*. 2020;5(2):e002067.
20. WHO. TDR: For research on diseases of poverty. Health Product Profile Directory 2021 [Available from: <https://www.who.int/tdr/diseases-topics/product-directory/en/>].
21. WHO. Target product profiles for needed antibacterial agents: enteric fever, gonorrhoea, neonatal sepsis, urinary tract infections and meeting report. Geneva: World Health Organisation; 2020. Contract No.: Licence: CC BY-NC-SA 3.0 IGO.
22. UNICEF, NEST360. Target Product Profiles for Newborn Care in Low-Resource Settings (v1.2): consensus meeting report, March 2020. 2020.
23. Foundation C. Accelerating Innovation for Mothers: Target Product Profiles Geneva, Switzerland: Concept Foundation; 2021 [Available from: <https://www.conceptfoundation.org/accelerating-innovation-for-mothers/target-product-profiles/>].
24. Cocco P, Ayaz-Shah A, Messenger MP, West RM, Shinkins B. Target Product Profiles for medical tests: a systematic review of current methods. *BMC Med*. 2020;18(1):119.
25. Vogel JP, Dowswell T, Lewin S, Bonet M, Hampson L, Kellie F, et al. Developing and applying a 'living guidelines' approach to WHO recommendations on maternal and perinatal health. *BMJ Glob Health*. 2019;4(4):e001683.
26. Souza JP, Gulmezoglu AM, Vogel J, Carroli G, Lumbiganon P, Qureshi Z, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. *Lancet*. 2013;381(9879):1747-55.
27. Attawattanakul N, P. T. Effects of antenatal dexamethasone on respiratory distress in late preterm infant: a randomized controlled trial. *Thai Journal of Obstetrics and Gynaecology*. 2015;23:25-33.
28. Ontela V, Dorairajan G, Bhat VB, Chinnakali P. Effect of Antenatal Steroids on Respiratory Morbidity of Late Preterm Newborns: A Randomized Controlled Trial. *J Trop Pediatr*. 2018;64(6):531-8.
29. Porto AM, Coutinho IC, Correia JB, Amorim MM. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. *Bmj*. 2011;342:d1696.
30. The Lancet Global H. Progressing the investment case in maternal and child health. *Lancet Glob Health*. 2021;9(5):e558.
31. Footman K, Chersich M, Blaauw D, Campbell OM, Dhana A, Kavanagh J, et al. A systematic mapping of funders of maternal health intervention research 2000-2012. *Global Health*. 2014;10:72.
32. Bhattacharya S, Innovation BHPCfRSa. Safe and Effective Medicines for Use in Pregnancy: A Call to Action. University of Birmingham; Birmingham, UK; 2021.
33. Hug L, Alexander M, You D, Alkema L, Estimation UN-aGfCM. National, regional, and global levels and trends in neonatal mortality between 1990 and 2017,

with scenario-based projections to 2030: a systematic analysis. *Lancet Glob Health*. 2019;7(6):e710-e20.

34. Murtagh M, Blondeel K, Peeling RW, Kiarie J, Toskin I. The relevance of target product profiles for manufacturers, experiences from the World Health Organization initiative for point-of-care testing for sexually transmitted infections. *Arch Public Health*. 2021;79(1):187.

35. Craciunas L, Pickering O, Chu J, Zurauskiene J, Coomarasamy A. Target Product Profile for an endometrial receptivity test: women's perspective. *Eur J Obstet Gynecol Reprod Biol*. 2020;253:42-7.

36. Husain MJ, Datta BK, Kostova D, Joseph KT, Asma S, Richter P, et al. Access to Cardiovascular Disease and Hypertension Medicines in Developing Countries: An Analysis of Essential Medicine Lists, Price, Availability, and Affordability. *J Am Heart Assoc*. 2020;9(9):e015302.

37. Medley N, Poljak B, Mammarella S, Alfirevic Z. Clinical guidelines for prevention and management of preterm birth: a systematic review. *BJOG : an international journal of obstetrics and gynaecology*. 2018;125(11):1361-9.

38. Stelzl P, Kehl S, Oppelt P, Maul H, Enengl S, Kyvernitakis I, et al. Do obstetric units adhere to the evidence-based national guideline? A Germany-wide survey on the current practice of initial tocolysis. *Eur J Obstet Gynecol Reprod Biol*. 2022;270:133-8.

39. Nazifovic E, Husslein H, Lakovschek I, Heinzl F, Wenzel-Schwarz E, Klaritsch P, et al. Differences between evidence-based recommendations and actual clinical practice regarding tocolysis: a prospective multicenter registry study. *BMC pregnancy and childbirth*. 2018;18(1):446.

40. Fox NS, Gelber SE, Kalish RB, Chasen ST. Contemporary practice patterns and beliefs regarding tocolysis among u.s. Maternal-fetal medicine specialists. *Obstet Gynecol*. 2008;112(1):42-7.

41. Shennan A, Suff N, Leigh Simpson J, Jacobsson B, Mol BW, Grobman WA, et al. FIGO good practice recommendations on progestogens for prevention of preterm delivery. *Int J Gynaecol Obstet*. 2021;155(1):16-8.

42. RANZCOG. Progesterone: Use in the second and third trimester of pregnancy for the prevention of preterm birth. Melbourne, Australia; 2017.

43. American College of O, Gynecologists' Committee on Practice B-O. Prediction and Prevention of Spontaneous Preterm Birth: ACOG Practice Bulletin, Number 234. *Obstet Gynecol*. 2021;138(2):e65-e90.

44. Administration USFD. CDER proposes withdrawal of approval for Makena 2020 [Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/cder-proposes-withdrawal-approval-makena>].

45. Coler BS, Shynlova O, Boros-Rausch A, Lye S, McCartney S, Leimert KB, et al. Landscape of Preterm Birth Therapeutics and a Path Forward. *J Clin Med*. 2021;10(13).

46. Foundation C. Medicines for pregnancy specific conditions: research, development and market analysis 2021 [Available from: <https://www.conceptfoundation.org/global-news/medicines-for-pregnancy-specific-conditions-research-development-and-market-analysis/>].

Box 1. Use case scenarios for TPPs in prevention of preterm birth and treatment of preterm labour

Prevention of preterm birth: A prophylactic agent that can be administered to pregnant women at increased risk of spontaneous preterm birth. The medicine can be administered in any healthcare setting where pregnant women receive care, would have an excellent safety profile during pregnancy, can be commenced early in pregnancy and can be continued throughout pregnancy, as required.

Management of preterm labour: A therapeutic agent that can be administered by skilled health personnel to pregnant women experiencing spontaneous preterm labour, accompanied by monitoring of maternal and fetal well-being in antenatal care settings. The therapeutic agent will inhibit uterine contractions, facilitate prolongation of pregnancy, be safe for women and babies, and ideally improve perinatal health outcomes.

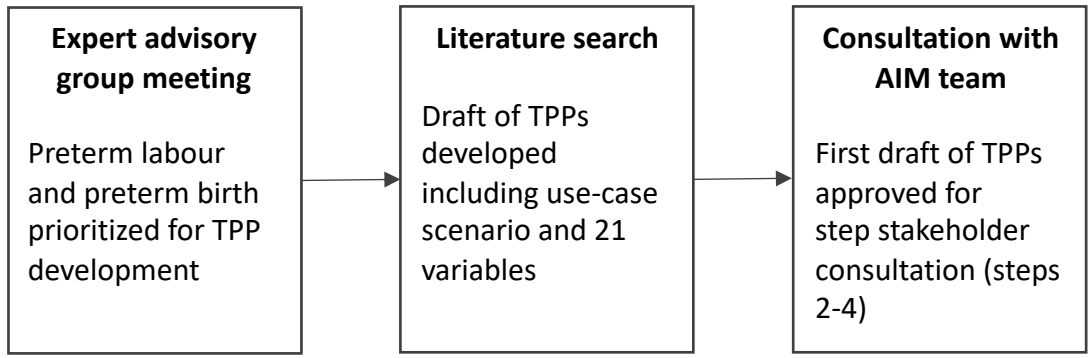
Figure 1. Overview of Target Product Profile development process**Figure 2 Stakeholders' distribution by WHO global regions**

The proportion of stakeholders who participated in the survey (n = 46) and interviews (n = 21), in each of the WHO global regions. AFR = African region (yellow), AMR = Region of the Americas (blue), EMR = Eastern Mediterranean region (dark green), EUR = European region (red), SEAR = South-East Asian region (light green), WPR = Western Pacific region (black).

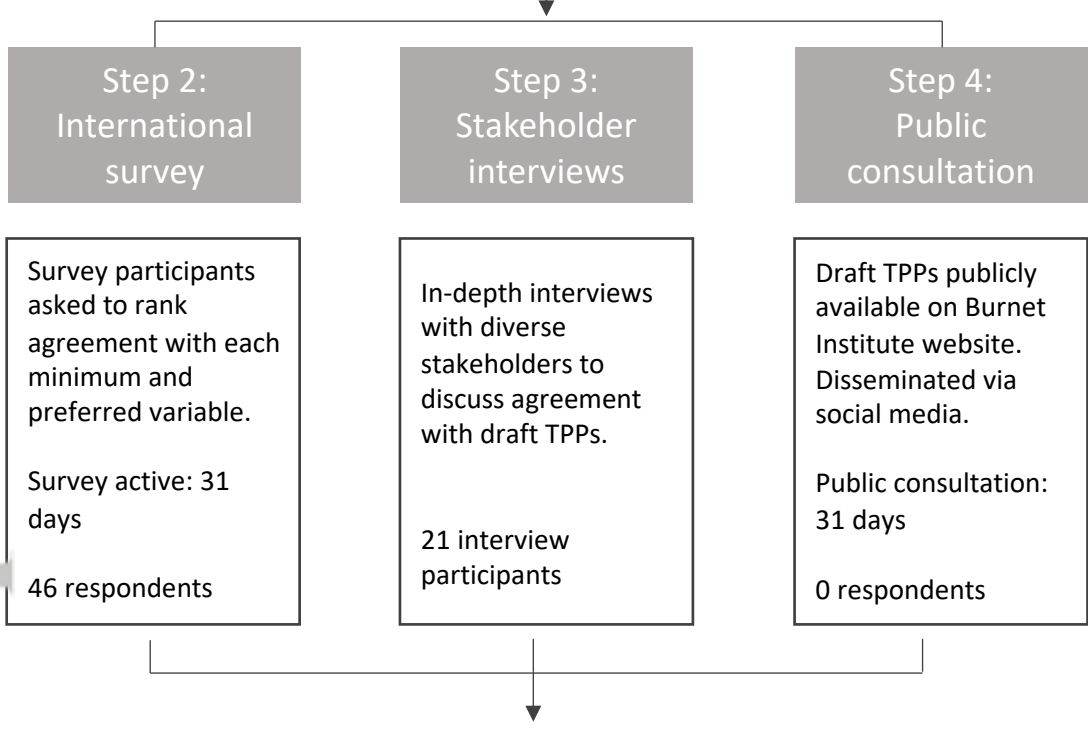
Figure 3. International survey responses

Results from international stakeholder survey. Percentage of respondents that strongly agreed (dark green), agreed (light green), were neutral (grey), disagreed (orange) or strongly disagreed (red) in response to the minimum and preferred requirements for each variable in the TPPs for new medicines to prevent preterm birth (A, B) and manage preterm labour (C, D). Black dotted line = consensus level

Step 1: Initial drafting phase



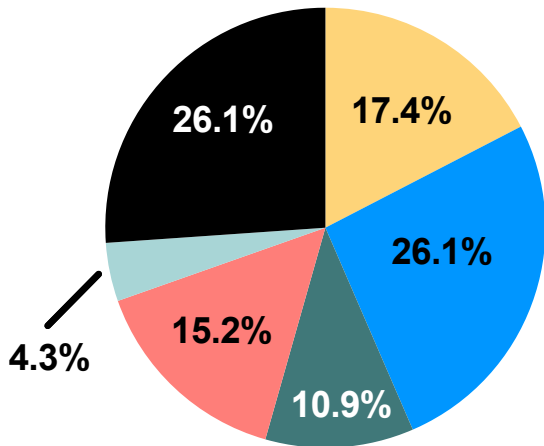
First draft of TPPs for consultation



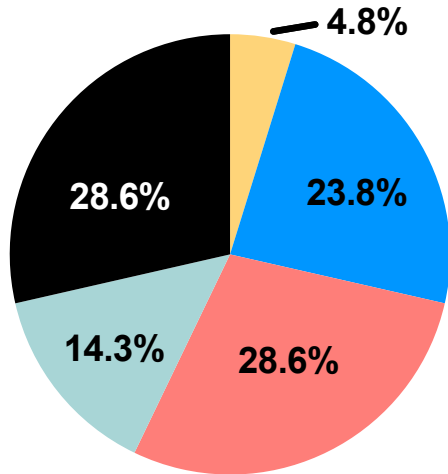
Step 5: Synthesis and finalisation

Quantification of survey results
Themes identified from interviews
Areas of disagreement refined
Final drafts of TPPs approved by expert advisory committee and made public

Survey

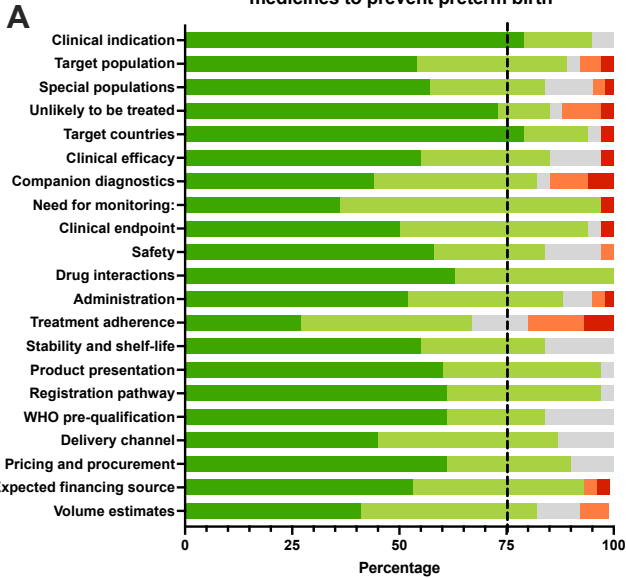


Interviews

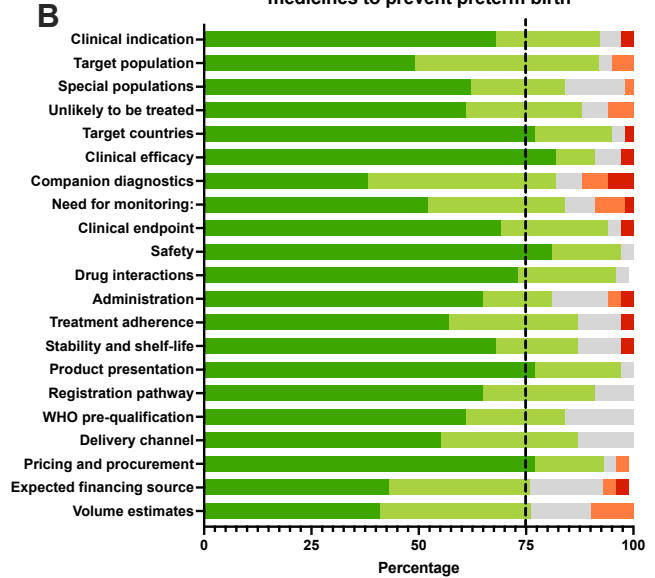


■ Strongly agree
■ Agree
■ Neutral
■ Disagree
■ Strongly disagree

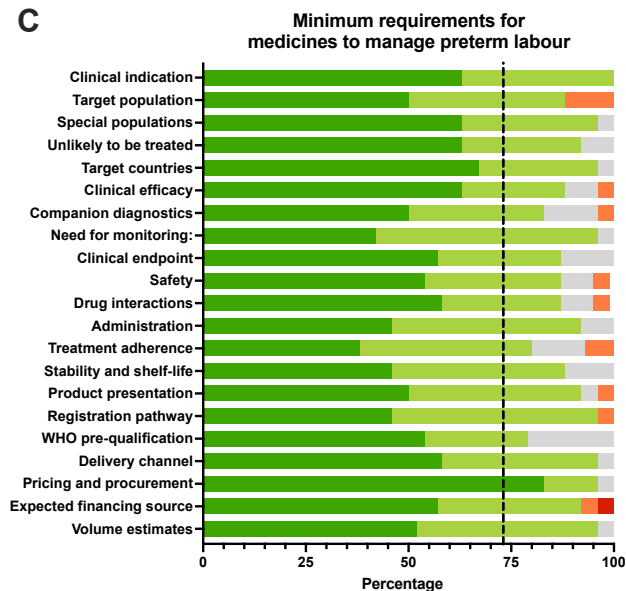
Minimum requirements for medicines to prevent preterm birth



Preferred requirements for medicines to prevent preterm birth



Minimum requirements for medicines to manage preterm labour



Preferred requirements for medicines to manage preterm labour

