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Development of A Target Product Profile (TPP) for a Diagnostic Test for Therapeutic Drug Monitoring of Meropenem

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Abstract

This protocol outlines the development of a Target Product Profile (TPP) for an in vitro diagnostic (IVD) test to enable therapeutic drug monitoring (TDM) of meropenem, a potent broad-spectrum beta-lactam antibiotic, often reserved for severe infections. By defining the key performance and operational characteristics required of a diagnostic test, this TPP aims to stimulate and direct the development of critically needed IVDs to address this unmet clinical need.

The expected outcome of this work is a consensus-driven TPP that reflects stakeholder input and identifies the minimal and preferred criteria for a fit-for-purpose TDM test. This TPP will serve as a blueprint for innovators, guiding the development of diagnostic technologies to optimise meropenem use, improve patient outcomes, and reduce antimicrobial resistance (AMR).

Introduction:

- 1 The increasing prevalence of antimicrobial resistance (AMR) to carbapenems, such as meropenem, poses a significant challenge in treating severe infections. AMR has a worsening burden of disease, with 5 million deaths associated with resistant infections globally in 2019 (Antimicrobial Resistance, 2022).
Meropenem is a potent broad-spectrum beta-lactam antibiotic, often reserved for severe infections. Significant meropenem pharmacological variability, particularly in the critically ill, and current one-size-fits-all doses, means that many patients are receiving inappropriate amounts of antibiotic, thus exacerbating AMR. The current strategy to suppress AMR is to limit use, rather than improve use. While limiting use may slow AMR, meropenem is essential for patient care. Furthermore, toxicity of meropenem is under appreciated, with 10–15% of ICU patients treated with beta-lactams, including meropenem, and over 50% of patients with trough concentrations above 64 mg/L, experiencing neurotoxicity (Imani et al., 2017).
Therapeutic drug monitoring (TDM), which involves measuring circulating drug concentrations and adjusting dosing to reach a pre-defined target serum concentration, offers a way to reduce AMR whilst improving health outcomes. However, TDM of meropenem is not routinely done due to the lack of suitable measurement technologies (e.g. liquid chromatography–mass spectroscopy (LC-MS)), which are expensive, requires specialist personnel, and most importantly is too slow to inform effective treatment decision making.
Following on from the pandemic, advances in diagnostic detection technologies are presenting new opportunities to accurately measure meropenem with short turnaround times in the laboratory, or if needed at the point of care. However, the exact design specifications and performance characteristics of such a test are unclear and present a market failure risk to potential innovators of new tests.
A Target Product Profile is a strategic document that outlines the key performance and operational characteristics that a new technology must meet to fulfil clinical, regulatory, and market needs. It serves as an aspirational blueprint, guiding the development of diagnostic tests by defining minimal (must-have) and optimal (nice-to-have) criteria, including unmet clinical needs, analytical performance, clinical performance, regulatory compliance, economic factors and operational requirements.
This protocol seeks to develop a Target Product Profile (TPP), to stimulate and direct the development of critically needed, fit-for-purpose *In Vitro* Diagnostic (IVD) Medical Devices for therapeutic drug monitoring (TDM) of meropenem.

Objectives:

- 2
 - Identify and define the key characteristics required for a reliable IVD for TDM of meropenem.

- Collect and integrate input from a broad range of stakeholders, ensuring that diverse perspectives are included to create a robust yet technically feasible TPP.
- Facilitate consensus building on the minimal and preferred criteria for the performance, usability, and cost of the diagnostic test.

Methodology:

- 3 This TPP will be developed according to the following methodology, which has been largely adapted from the standard WHO procedure and the framework of Cocco, *et al* (Cocco et al., 2021)
- A multidisciplinary TPP Development committee will be established, consisting of experts and key stakeholders from relevant disciplines. The committee will be chaired by Dr Kerrie Davies and Dr Richard Gould and facilitated by two experienced TPP development consultants (Messenger, Osborn).
- To ensure broad and inclusive engagement, the TPP committee will recruit members from diverse and relevant disciplines, including clinicians, laboratory scientists, pharmacists, meropenem TDM experts, public health officials, regulatory experts, reimbursement agencies, professional bodies, patient advocates and end users. To minimise the risk of bias from stakeholder recruitment, members will be identified and approached on the basis of either 1: their representation of key stakeholder groups/organisations in the field, as identified by the Chair and Deputy Chair; or 2. Identification of academic key opinion leaders through publication and citation analysis using Web of Science and the search terms ["Therapeutic Drug Monitoring" AND Meropenem], the top 10 most published and cited authors globally and any UK academics identified in the top 25 will be approached to participate. The selection process will aim to recruit between 10–30 committee members and be inclusive of gender and underrepresented groups.
- All members will be required to declare any potential conflict-of-interests following a standard form and process, these will be reviewed by the committee Chair and Deputy Chair and final decisions on participation determined by the Chair. Any members with major conflicts of interests will be excluded from participation and all declarations will be made available in any final publication.
- TPP development meetings will be deemed quorate if more than 50% of members are in attendance. Any committee members who do not respond to the Delphi like surveys within 14 days and up to two reminders will be excluded from future participation.
- A scoping review of the current literature will be conducted to inform the initial TPP scoping and draft. This review will aim to identify any relevant TPPs and recent systematic reviews on meropenem therapeutic drug monitoring. Insights into clinical unmet needs and preferences will also be drawn from an independent survey of clinicians, pharmacists and laboratory scientists, currently ongoing and due to report in December 2024.
- The first meeting of the TPP development group will aim to verify the findings from the scoping review and to align upon the scope of the TPP. It will also seek agreement on

the priority characteristics to be included in the initial TPP Draft. From this a draft TPP will be developed using these initial insights and outputs from the review to populate. An iterative Delphi-like process will then be used to refine the draft and achieve consensus among the TPP development committee. Prior to the first consensus meeting, members will be sent an electronic survey to evaluate each minimal and preferred characteristic criterion, rating them on a 4-point Likert scale (1, fully disagree; 2, mostly disagree; 3, mostly agree; 4, fully agree; members can also mark "No opinion"). The threshold for consensus will be set *a priori* at 75% agreement. Members will be invited to comment on all characteristics but will be required to elaborate when they do not agree (Likert score 1 or 2). All comments received will be compiled and jointly reviewed by the Chairs and facilitators, and the TPP revised (if necessary) to address criticisms, incorporate suggestions, and avoid misunderstandings of intent. Revised characteristics will be discussed and amended at the consensus meeting.

The revised draft of the TPP will be made available for public consultation and promoted by committee members via e-mail and social media (LinkedIn), feedback from industry and test developers will be specifically sought, but considered independently from other feedback. The public consultation will aim to receive feedback from at least 50 respondents, or be extended for up to a total of 28 days. Comments will be collected through an online survey, compiled and jointly reviewed by the Chairs and facilitators, and the TPP revised to address criticisms, incorporate suggestions, and avoid misunderstandings of intent. Responses from the public consultation and any suggested changes to characteristics will be shared with members and discussed at the final consensus meeting. Any revised characteristics will be circulated for a final round of Delphi, however characteristics not achieving 75% agreement at this stage will not be further refined and either excluded or noted as such in any final publication, with narrative provided to justify the disagreement between members.

To ensure full transparency of reporting, the results of the delphi-surveys (including % agreement and response counts) and the public-consultation, will be published alongside the final TPP characteristics.

Dissemination:

- 4 The finalised TPP will be published in a peer reviewed academic journal. It will be promoted through academic channels, social media, and targeted outreach to industry and regulatory bodies to ensure broad visibility and use by researchers, clinicians, and diagnostic test developers.



Protocol references

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