A Modern Curriculum for Training Scientists in Model-Informed Drug Development: Progress Report on FDA Grant to Train Regulatory Scientists

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Under US Food and Drug Administration (FDA) grant (2U18FD005320-06), the Critical Path Institute (C-Path) and experienced private sector partners collaborated with global health organizations to create didactic video materials in an e-learning format on model-informed drug development (MIDD) topics relevant to a non-modeling audience. Several multinational pharmaceutical companies contributed case studies illustrating the application of the MIDD approach in practice. Training videos were created and divided into several modules: introducing the MIDD landscape for drug development and regulatory science, a review of various model types used for MIDD, discussions of how models inform drug development and regulatory decisions, future goals of MIDD, and discussions on the interconnectedness of models used for MIDD. Examples and vignettes from stakeholders and thought leaders were included. These educational materials fill a gap between academic and "on the job training" for regulators, academic, and industry scientists, delivering insights and value for those performing modeling and non-modelers reviewing the output of modeling and simulation work. A total of 13 hours of video content is currently available. A small panel of FDA reviewers is currently beta-testing the learning management system (LMS). Future efforts for this MIDD training initiative will include expansion of the content via an expanded and diverse faculty, 1:1 online mentorship sessions, and eventually broader access to this resource consistent with an open science approach and curriculum. The MIDD training LMS can accommodate a diverse learning ecosystem; further development may also accommodate different audiences in the future.

Model-informed drug development (MIDD) has been an important part of the drug development paradigm for more than 2 decades and has been embraced by academic, industry, and regulatory scientists.[1–3] MIDD approaches use a variety of quantitative methods to help balance the risks and benefits of drug products in development. When successfully applied, MIDD approaches can improve clinical trial efficiency, increase the probability of regulatory success, and optimize drug dosing/therapeutic individualization in the absence of dedicated trials. MIDD was formally recognized in Prescription Drug User Fee Act (PDUFA) VI.[4] There have been many regulatory applications of MIDD to address a variety of drug development and regulatory questions. During development, MIDD strategies encompass a variety of model types as tools to inform different decision points and problems, ideally in an integrated and complementary manner.[5] Each model type offers a different approach and may be constructed on different data. They can inform different problems or may be used together to offer fidelity to a particular decision (assuming they make the same recommendation). Often, model types evolve in parallel and inform each other, and may be used interchangeably.

Global regulatory authorities have embraced the MIDD approach and have provided guidance and support for its use among a diverse group of stakeholders. In addition, the Center for Drug Evaluation and Research (CDER) of the US Food and Drug Administration (FDA) has undertaken multiple initiatives to facilitate the MIDD mission.

The FDA has been conducting an MIDD Pilot Program to facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources as well as further promoting the approach and active communication with sponsors.[6] Of course, the expanded effort to conduct and report on MIDD-based activities also increases the necessity of education and training in this approach. Training needs go beyond the practitioners as well. The multidisciplinary aspects of the modern, team-based approach to well-conducted MIDD projects necessitates training on multiple levels.[7,8] Many practitioners of the approach have hybrid backgrounds and are cross trained in both quantitative and life sciences with others being more heavily concentrated in one or the other. The curriculum content for hands-on scientists in this field has been the subject of

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much discussion[9–11] and there is more-recent appreciation that education must also be extended to those who embrace the discipline in various related contexts, although not directly as practitioners. It is in this vein that the FDA has sought to provide a training curriculum about MIDD for translational scientists that participate in various contexts of drug or biologic regulatory review and may encounter MIDD assets by sponsors seeking approval. It is in this context that the FDA issued a request for proposals and grant mechanism by which funding could be provided for such curriculum and is also the basis for the presentation of the initial offering provided herein. The purpose of this paper is to raise awareness to this initiative and its progress, invite critique of the initial offering, and invite additional collaborators to further expand and refine the content so that it can better achieve its purpose and serve the MIDD community.

METHODS

Under FDA grant (2U18FD005320-06), the Critical Path Institute (C-Path) and experienced private-sector partners from Certara, Metrum and several multinational pharmaceutical companies collaborated with global health organizations like the Bill & Melinda Gates Foundation and Pharmacometrics Africa to create didactic video materials in an e-learning format on MIDD topics relevant to a non-modeling audience. Several pharmaceutical companies (Sanofi, Genentech/Roche, and AstraZeneca) contributed materials illustrating the application of the MIDD approach in practice as learning examples. **Table 1** provides a listing of the current Steering Committee members as well as those who contributed content to the initial training curriculum. The FDA reviewed the training material slide content with the Steering Committee and once alignment was verified, videotaping of the lectures commenced. An important focus for the Steering Committee was to ensure that each lecture conveyed how modeling and simulation activities should be interpreted and valued by a translational scientist who may not have hands-on expertise but needs to appreciate the effort and impact of the approach, analyses, and conclusions as part of a submission deliverable. The Steering Committee reviewed all content from the outline to slide creation and finally video production to advise on harmonization of style and flow. During the initial launch phase of the learning management system (LMS) platform additional feedback will be garnered from the initial trainee class and materials may be further refined.

A 6-month evaluation of various LMS vendor's systems was conducted prior to selection. The selection phase was guided by predefined requirement attributes set forth by the Steering Committee and included cost, hosting capabilities, security, access, and content capacity.

RESULTS

Course content categories were initially defined by the FDA and refined by faculty represented on the Steering Committee. The course consists of an introduction and eight modules, each containing a slide-show presentation with voice-over recording. In total, the training course contains over 30 individual presentations with over 13 hours of recorded content that was reviewed by the FDA.

The MIDD training course is hosted on a user-friendly, customizable, LMS developed by Docebo[12] and was purchased using C-Path grant funds. This platform provides an intuitive user interface that allows the learner to navigate several modules of course content easily and efficiently. The LMS is capable of generating a course catalog, learning plan, customizable user-reports, assessment tools, and the ability to upload individual videos up to 800 Mb in size. Administrators can enroll users into a single module or can grant access to the entire curriculum. The LMS provides a secure web-based environment for the materials and serves as a hub for additional content. **Figure 1** show screen shots of the MIDD LMS highlighting its access and navigation. Additional screen shots of the current MIDD LMS with emphasis on access, content selection, and post course evaluation are contained in **Figure 2a–c**. There is a high degree of customization possible with the setup and

Table 1 Initial MIDD training material contributors

Non-profit partners	Industry and CRO partners	Regulatory partners
Critical Path Institute • Jeff Barrett, PhD[a] • Klaus Romero, MD, MS[a] • Jagdeep Podichetty, PhD • Sakshi Sardar, PhD	Astellas • Stacey Tannenbaum, PhD[a]	FDA • Issam Zineh, Pharm.D., PhD • Qi Liu, PhD[a] • Rajanikanth Madabushi, PhD[a]
BMGF • Steve Kern, PhD[a]	Astra Zeneca • Dinko Rekic, PhD, MS	
PMx Africa • Colin Pillai, PhD[a]	Certara • Craig Rayner, Pharm.D., MBA[a] • Amy Cheung, PhD • Rajesh Krishna, PhD • Adekemi Taylor, PhD • Rik de Greef, MS	
	Genentech/Roche • Pascal Chanu, Pharm.D. • Chi-Chung Li, PhD, MS	
	Metrum • Marc Gastonguay, PhD[a]	
	Sanofi • Graham Lockwood, PhD	

CRO, Clinical Research Organisation; FDA, US Food and Drug Administration; MIDD, model-informed drug development.
[a]Steering Committee Members.

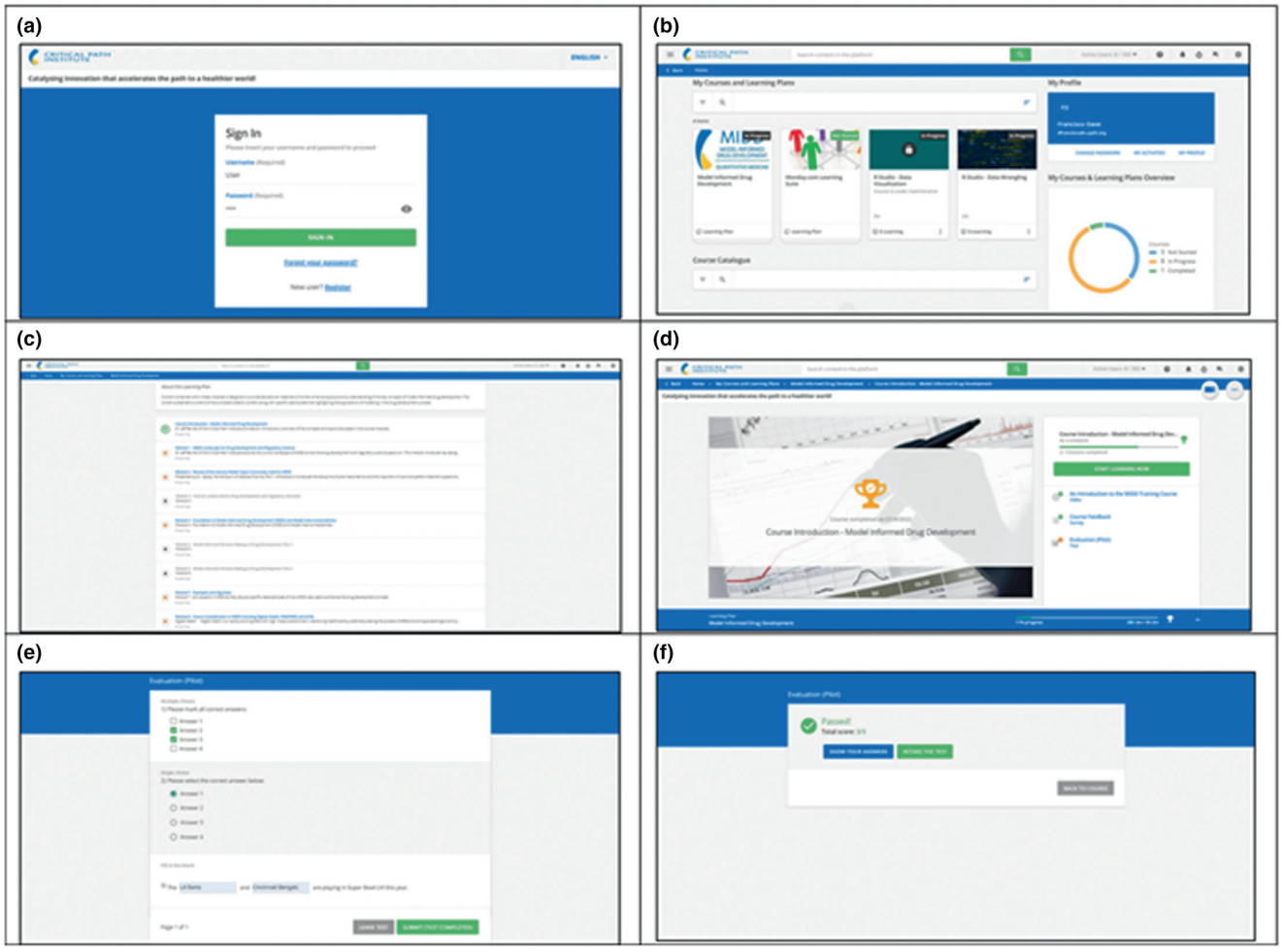

Figure 1 Screen Shots of the MIDD Learning Management System: (**a**) Sign-in page, (**b**) LMS Course Selection screen, (**c**) Module Selection window, (**d**) Module-Start Screen, (**e**) Module evaluation screen and (**f**) Module evaluation score. LMS, learning management system; MIDD, model-informed drug development.

the system is customizable to the end-user from the standpoint of screen orientation and multitasking requirements.

User-experience, course feedback, Q&A capabilities, and content suggestions are assessed using an integrated comment section, message board, and post-module evaluation tool in the LMS. The catalog of current training content available on the LMS is shown and described in **Table 2**. The lectures provide a foundation for the MIDD approach, illustrate the context for which the approach influences decision making both within a company and to regulatory authorities, and ultimately how the approach provides confidence in these decisions. Fundamental to the MIDD approach is the description and utilization of modeling and simulation for this purpose and how models and decisions can be interconnected. Most importantly, the occasions that a reviewer might encounter the various approaches and their outputs are described.

DISCUSSION

Future efforts for this MIDD training initiative will include expansion of the content via an expanded and diverse faculty, 1:1 online mentorship sessions between trainees and faculty, and eventually broader access to this resource consistent with an open science approach and curriculum. More sophisticated and complex content will eventually be added to the curriculum based on the direction of the Steering Committee and the FDA input.

Measuring the impact of the training curriculum will be undertaken at several levels. The first, most obvious, metric is to simply assess the number of scientists who complete any portion of the training material with drill down to their assessments of the value in post course surveys. Pre and post-testing capabilities are provided in the LMS and can be incorporated into assessments of comprehension. The nature of the questions posed during the 1:1 sessions may provide a more granular understanding as well, especially with categorization of the questions and assessment of information value. Outreach to global stakeholders will be pursued once the initial refinement phase and additional capacity testing is complete. Recent presentations at the World Conference of Pharmacometrics in 2022[13,14] highlighted both the enthusiasm for the curriculum and the interest in expanding the content further. It is expected that the MIDD/LMS will be provided as a resource

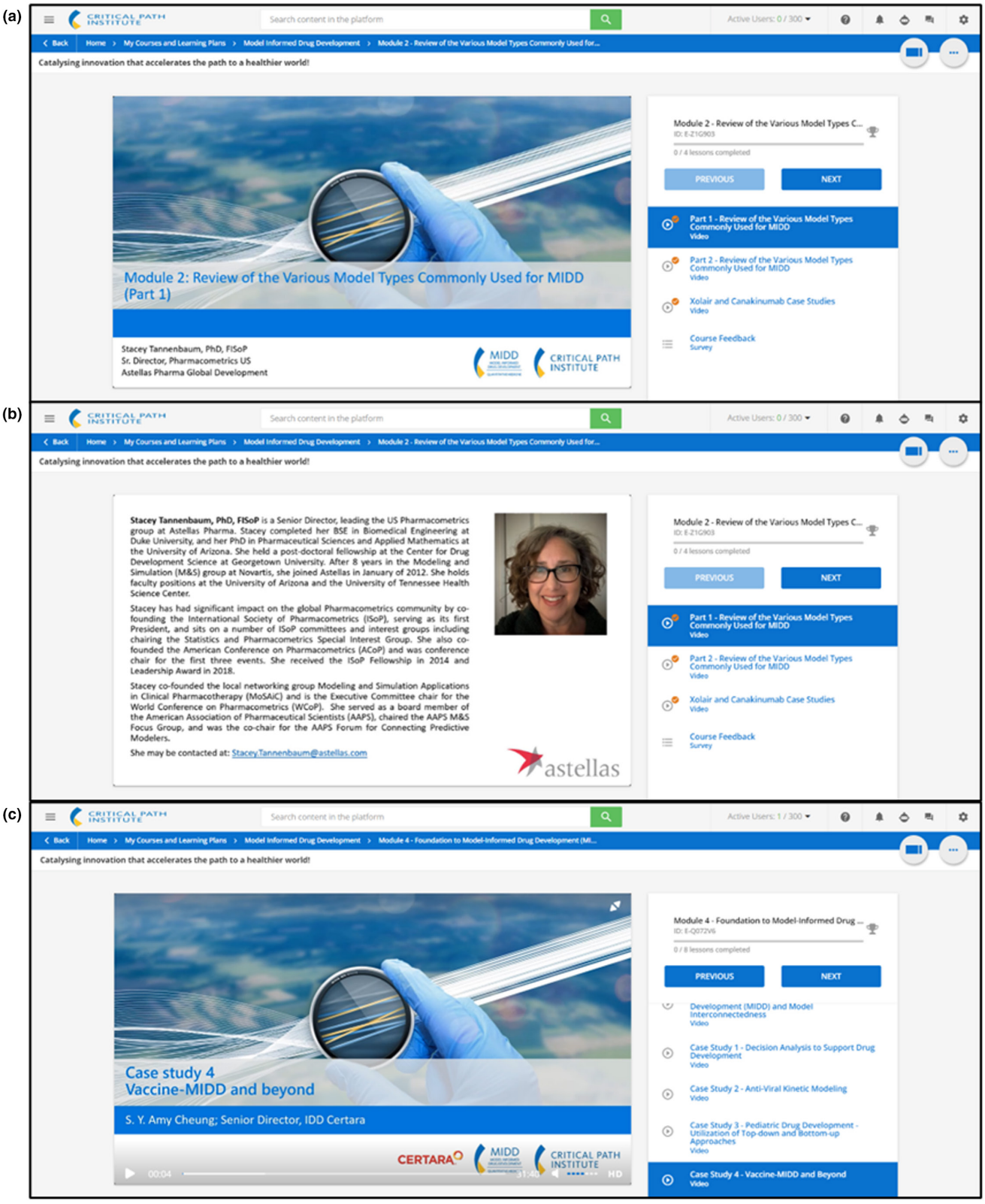

Figure 2 Screen shot showing the launch of an individual training module (**a**) with the slide and video content review (**b, c**) once the module is launched.

Table 2 Catalogue of initial MIDD training material content

Section, title (duration)	Lecturer (contributor)	Content
Course introduction (18 minutes)	Barrett (C-Path)	Description of the hype vs. reality about MIDD; discussion of models vs. data and value creation. Some description of the key stakeholders and MIDD equivalent approaches in other fields/industries with an assessment of how training in MIDD will impact a reviewer's day-to-day activities
Module 1: MIDD landscape for drug development and regulatory science (39 minutes)	Barrett (C-Path)	Background describing MIDD in general, its context for use in the pharmaceutical industry including the support from global regulatory authorities and an ever-expanding stakeholder community. Critical decisions made by sponsors during drug development are reviewed as well as interdependencies of decisions and decision-making hierarchy
Module 2: Review of the various model types commonly used for MIDD (2 hours 23 minutes)	Tannenbaum (Astellas)	Causal chain of various functional relationships that drive many of the interconnected model types; specific model types linked to milestone decisions and fit-for-purpose efforts; guidance and other motivations/incentives
Module 3: How do models inform drug development and regulatory decisions (42 minutes)	Pillai (CP+ Associates)	Review of context for decision making comparing sponsor/industry perspectives with regulator perspectives. A review of MIDD in pediatric drug development and summary of considerations for clinical reviewers
Module 4: Foundations to MIDD and Model Interconnectedness (2 hours 48 minutes)	Rayner (Certara)	MIDD approach linked to various stakeholder communities including patients; engagement and interconnectedness; tools and principles; applications
Module 5/6: Model Informed Decision Making in Drug Development (2 hours 52 minutes)	Gastonguay (Metrum)	MIDD investment related to decision making impact; strategy, benefits, and challenges
Module 7: Examples and Vignettes (1 hour 13 minutes)	Sanofi (4 vignettes recorded)	• Eliglustat (Gaucher Disease): PBPK modeling used to reduce number of DDI studies and optimize dosing • Isatuximab (Relapse Refractory Multiple Myeloma): PopPK, exposure response, disease and joint modeling supported internal decision making on dosing • Caplacizumab (Acquired Thrombotic Thrombocytopenic Purpura): Model–based dosing recommendations in pediatric patients with aTTP • SAR442257 (Multiple Myeloma): Utilization of QSP modeling to predict safety and efficacy of a tri-specific T cell engager antibody for multiple myeloma before FIH
	AstraZeneca (1 vignette recorded)	• AZD8233 (Hyperlipidemia): MIDD increased confidence in efficacy during single ascending dose study, reducing risk; 6-month time savings by enabling Ph2 start prior to multiple ascending dose study completion
	Genentech/Roche (2 vignettes recorded)	• Mircera (chronic kidney disease): PBPK using RWD used to optimize clinical trial design and reduce number of pediatric trial participants • Mosuntuzumab (non-Hodgkin lymphoma): PK and QSP used to validate exposure metric to generate supportive evidence for efficacy and inform Ph2 dose selection in addition to mitigating risk of cytokine released syndrome for T-cell dependent bispecific antibodies
Module 8: Future goals of MIDD: Digital Health, AI/ML and RWD/RWE (2 hour 17 minutes)	Podichetty, Sardar, Beheshti, Burton, Aggarwal, and Barrett (C-Path)	Explanation of where is MIDD growing with respect to new methodologies and approaches including digital health initiatives, RWD and RWE and AI and ML with projection on where a reviewer is likely to see this, when and in what context

AI, artificial intelligence; C-Path, Critical Path Institute; DDI, drug-drug interaction; FIH, first in human; MIDD, model-informed drug development; ML, machine learning; PBPK, physiologically-based pharmacokinetic; PopPK, population pharmacokinetic; QSP, quantitative systems pharmacology; RWD, real-world data; RWE, real-world evidence.

for the entire global MIDD community. The public release of the MIDD/LMS is planned for September 18, 2023, after which time details of the access to the platform will be provided to the global community by the C-Path. Training certification will likely be a future goal of this initiative as well.

It is the intention of the Steering Committee that this initial training curriculum will continue to grow and evolve to represent a broader stakeholder community both in terms of the diversity of the content as well as the audience that would have access to the training. The MIDD approach and implementation are not static and likewise the training materials should continue to stay in step with the discipline. The underlying core disciplines that support the approach, including pharmacology, engineering, medicine, and statistics, will certainly also benefit from the MIDD outgrowth and application, and will presumably seek to promote quantitative scientists that become MIDD practitioners in addition to offering their own take on the discipline as it evolves. Here too, we envision this curriculum as a sustaining material for future growth. Interested stakeholders are encouraged to contact any member of the Steering Committee to propose additional training content for addition to the MIDD training LMS. The nature of these proposals can include both content suggestions for the Steering Committee to outsource or actual materials that the stakeholder wishes to put forward for potential inclusion. Pending further evaluation by the Steering Committee these materials and access to the MIDD training site LMS will be extended to the broader ecosystem.

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CONFLICT OF INTEREST
The authors declared no competing interests for this work.

PRINCIPAL INVESTIGATOR'S (PI) STATEMENT
The authors confirm that the Jeffrey S. Barrett, PhD, FCP, is the PI responsible for this research and analysis.

DATA AVAILABILITY STATEMENT
Data generated herein for this analysis is based on literature and web-review but are available from the corresponding author upon request.

1. Zhang, L., Allerheiligen, S.R., Lalonde, R.L., Stanski, D.R. & Pfister, M. Fostering culture and optimizing organizational structure for implementing model-based drug development. *J. Clin. Pharmacol.* **50**(9 Suppl), 146S–150S (2010).
2. Marshall, S. *et al*. Model-informed drug discovery and development: current industry good practice and regulatory expectations and future perspectives. *CPT Pharmacometrics Syst. Pharmacol.* **8**, 87–96 (2019).
3. Lesko, L.J. Perspective on model-informed drug development. *CPT Pharmacometrics Syst. Pharmacol.* **10**, 1127–1129 (2021).
4. Wang, Y., Zhu, H., Madabushi, R., Liu, Q., Huang, S.-M. & Zineh, I. Model-informed drug development: current US regulatory practice and future considerations. *Clin. Pharmacol. Ther.* **105**, 899–911 (2019).
5. Stone, J.A. *et al*. Model-based drug development survey finds pharmacometrics impacting decision making in the pharmaceutical industry. *J. Clin. Pharmacol.* **50**(9 Suppl), 20S–30S (2010).
6. FDA Pilot Program <https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program>
7. Ho, K. *et al*. Making interprofessional education work: the strategic roles of the academy. *Acad. Med.* **83**, 934–940 (2008 Oct).
8. Wald, H.S., Davis, S.W., Reis, S.P., Monroe, A.D. & Borkan, J.M. Reflecting on reflections: enhancement of medical education curriculum with structured field notes and guided feedback. *Acad. Med.* **84**, 830–837 (2009).
9. Holford, N. & Karlsson, M.O. Time for quantitative clinical pharmacology: a proposal for a pharmacometrics curriculum. *Clin. Pharmacol. Ther.* **82**, 103–105 (2007).
10. Barrett, J.S. Applying quantitative pharmacology in an academic translational research environment. *AAPS J.* **10**, 9–14 (2008).
11. Barrett, J.S., Fossler, M.J., Cadieu, K.D. & Gastonguay, M.R. Pharmacometrics, a multidisciplinary field to facilitate critical thinking in drug development and translational research settings. *J Clin. Pharmacol.* **48**, 632–649 (2008) Published in Chinese Journal as well Chinese J Clin Pharmacol Ther. 13(5): 481–493, 2008.
12. "Docebo 7.5 Debuts Artificial Intelligence Sparking the Future of Enterprise Learning – Docebo." Docebo. Retrieved 2022-4-22 .
13. WCOP 2022 Regulatory Roundtable <https://www.sahpra.org.za/event/3rd-world-conference-on-pharmacometrics-wcop/>.
14. Barrett, J. *et al*. <https://wcop2022.org/2022/02/22/a-modern-curriculum-for-training-scientists-in-model-informed-drug-development-midd-initial-proposal-developed-in-support-of-fda-grant-to-train-regulatory-scientists/>