SUMMIT ON THE FUTURE OF CLINICAL TRANSLATIONAL PHARMACOLOGY

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Framing Document

Authored by:

ASCPT Summit Task Force

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Introduction

ASCPT is organizing a Summit on **The Future of Clinical Translational Pharmacology,** bringing together key thought leaders and stakeholders to i) envision the future of the clinical translational pharmacology discipline, ii) identify opportunities to realize its full potential, and iii) develop an action plan for how we could achieve this within the next decade. The central question will be**: Leaving no patient behind: how can clinical translational pharmacology seize the opportunity to maximize benefit and safety for every patient, advance health equity, and promote global health?**

The term 'clinical translational pharmacology' is deliberately used here as a broader, more dynamic term than 'clinical pharmacology', reflecting the evolving scope of the multidisciplinary field in the modern scientific, medical, and technological landscapes. In addition, the word 'translational' underscores the bidirectional bridge between scientific discoveries and application in clinical practice across the drug discovery, development, regulation and utilization (DDRU) continuum.

This framing document aims to provide succinct insights into the clinical translational pharmacology discipline, its value and impact, its multidisciplinary identity, the emerging science and technologies that may propel the discipline forward. The framing document also introduces briefly existing opportunities and challenges, to aid discussions at the Summit. Selected references for further in-depth reading are provided here.

Clinical Translational Pharmacology

Clinical translational pharmacology is arguably among the most dynamic fields in biomedical science. This dynamism results from the interplay of three factors: 1) the broad range of scientific roles that build on the discipline of clinical translational pharmacology; 2) the diverse knowledge, skills, and experiential backgrounds of clinical pharmacologists; and 3) the depth and breadth of clinical translational pharmacology's application space. Clinical translational pharmacology professionals catalyze advances in science through biomedical research, drive the development of promising new treatments for patients, inform regulatory assessment of investigational new therapies, expand the utilization of both new and existing drugs across all patient populations, inform public health policy, and apply these principles to advance therapeutics in global health setting. These scientists may have a medical or pharmacy degree but could also come with a background in translational science or bioengineering. The range of clinical translational pharmacology activities and applications are connected across the DDRU continuum including supporting global public health (**Figure 1**).

It has been argued that the protean nature of clinical translational pharmacology itself (a strength in many ways), along with the diverse settings in which clinical translational pharmacology is practiced, presents two of its greatest challenges: identity and competition. With respect to identity, the clinical pharmacologist can be found engaging anywhere and everywhere on the "translational sciences spectrum" including preclinical research, clinical research, clinical implementation, and public health. Within each of these spaces, there may be any number of scientific "subspecialties" in which a clinical pharmacologist might have domain expertise. These might incorporate, for example, the following knowledge areas: biopharmaceutics, drug disposition, measures/methods for assessment of drug activity, biomarker science, data science, quantitative methods, statistics, drug safety science, clinical trial methods, population science, policy development, implementation and evaluation, pharmacotherapy and pharmaeconomics. As a clinical translational pharmacologist tends to also have a generalist perspective with working knowledge about many scientific areas, it could lead to competition with scientists within subspecialties who may have deep domain expertise but may not have the breadth of experience around the clinical translational pharmacology application areas. It is consequently difficult to "pin down" a consensus, all-encompassing definition of what a clinical translational pharmacologist *is*—as evidenced by the perennial efforts to do just that every few years or so.

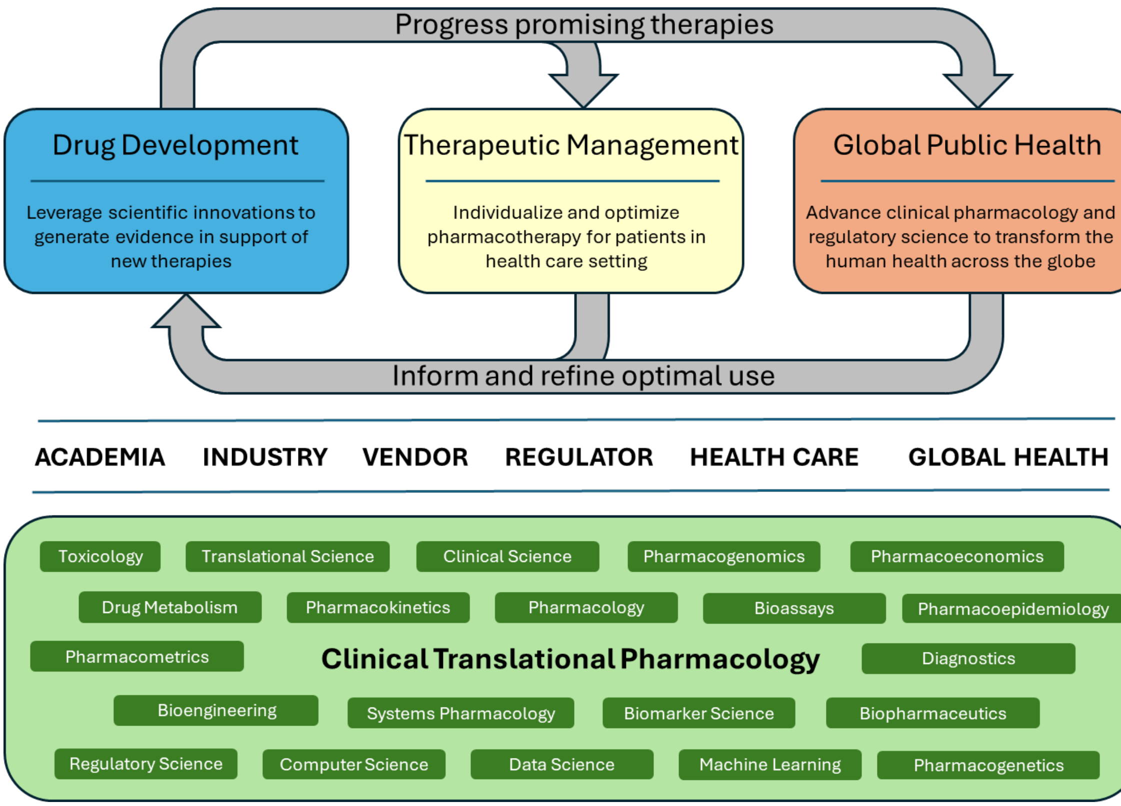

Figure 1: *The clinical translational pharmacology discipline plays a large role in drug development, therapeutic management and global public health by progressing promising therapies and informing and refining their optimal use. Clinical translational pharmacology professionals bring their skills and experience into a large variety of roles across wide range of professional organizations and possess a multidisciplinary skill set that builds on expertise across many scientific areas (adapted from Zineh and Hartman).*

Instead, the more instructive exercise has historically been to describe what a clinical translational pharmacologist *does* (and how) throughout the DDRU continuum. Clinical translational pharmacology can be seen as a patient-centered discipline that has the discovery, development, and optimal use of therapeutics for all patients, which is not limited just to dose optimization, as its major impetus. As such, the clinical translational pharmacologist is a scientist who has as their primary focus the development and optimization of therapeutic modalities, the delivery (dosing route and/or formulation) of therapeutics to patients, and the continual refinement of our understanding of drug response variability impacting benefit/risk that enables patient-specific decision-making. This unified purpose supported by a wide range of skills and professional roles makes clinical translational pharmacology a very versatile and unique discipline.

Impact along The DDRU Continuum

The potential and actual impacts of clinical translational pharmacology on drug DDRU are impossible to adequately summarize. Clinical translational pharmacology has been long recognized as **a critical and integrating discipline in the discovery and development of new therapeutics**. In fact, as an enterprise, clinical translational pharmacology dates to the earliest known examples of isolating pharmacologically active compounds for medicinal use in indigenous cultures. In the modern era, clinical translational pharmacology has transformed the way therapeutic products are developed, evaluated from the regulatory perspective, and individualized during therapeutic use. When we look at some of the determinants of success in drug development, for example, it is easy to recognize the critical role of pharmacological first principles in **increasing the chances an investigational new drug advances** from preclinical experimentation to early and later phases of clinical development. These include the importance of robustly characterizing and assuring pharmacological engagement with relevant biological target(s); ensuring adequate bioavailability in the relevant target tissue; development and utilization of pharmacologically-relevant biomarkers; characterizing the relationship between drug pharmacokinetics (PK) and pharmacodynamic (PD) effects (i.e., PK/PD relationships) in non-clinical and clinical contexts; evaluating the potential for adverse events through assessment of secondary pharmacology and drug target liability; selecting patient populations most likely to demonstrate a meaningful clinical response ; identifying patients most likely to demonstrate favorable benefit/risk profiles based on understanding of pharmacological mechanism relative to disease biology; and derisking therapeutic liability by characterizing the likely effect of “intrinsic” and “extrinsic” factors on treatment response variability.

Clinical translational pharmacology tools and approaches have also been brought to bear to **increase efficiency and reduce costs in drug development**. For example, drug developers who engage with regulatory bodies (e.g., the US FDA, EMA, PMDA) to explore the potential for incorporating quantitative pharmacology approaches in their drug development programs, utilizing a wide range of non-clinical, clinical and real-world data, have resulted in reduced clinical development times, more informed go/no-go decision-making, and millions of dollars in cost savings. Furthermore, clinical translational pharmacology tools and approaches have been critical to **enabling access to promising new treatments** by facilitating **extrapolation of findings from one well-studied context to another unstudied (or insufficiently studied) context** (e.g., extrapolation from adult to pediatric patients; extrapolation from one disease stage to another). In addition, clinical translational pharmacology has facilitated mechanistically- and quantitatively informed strategies to advance drug development and regulatory evaluation in therapeutic areas of high unmet medical need and in spaces in which drug development has been historically challenging such as in rare diseases and within the global health setting. Throughout the decades, clinical translational pharmacology has been instrumental in **addressing both the *scientific* and *operational* challenges which have been rate-limiting** in drug development and regulatory assessment of new therapies.

From the standpoint of therapeutic utilization, clinical translational pharmacology (in the forms of patient-oriented research and pharmacy practice) has been a major driving force in some of the advancements seen in the last several decades. Advances in our understanding of molecular biology and pharmacology have led to more pathway-specific drug development and novel modalities (e.g. complex biologics and cell and gene therapies), focusing drug development on ever-more refined disease subsets of patients (e.g. **precision medicine**). Coupled with clinical translational pharmacology research in genomics, this has led to the identification of patients using companion diagnostics. Moreover, the ability to innovate through providing new dosing strategies through new formulations or route of administration have led to **better utilization of medicines in low- and middle-income countries** for which health care access and cold storage is not readily available.

At the level of the individual patient, dose optimization through PK/PD modeling and **therapeutic drug monitoring** has led to more patient-specific tailoring of dosing regimens. Clinical translational pharmacology's focus on specific populations has been instrumental in making access possible and **improving outcomes in a wide range of patient groups** including pediatric patients, older adults, overweight and obese patients, pregnant or breast-feeding women, and other under-served or under-studied populations. Furthermore, research into drug interactions and patient-specific factors (e.g., renal and hepatic function) throughout the product lifecycle has deepened our understanding of conditions for **safe use and informed safer prescribing practices**. At the population level, pharmacoepidemiologic and pharmacovigilance approaches have allowed for the tracking and managing of risk and **comparative effectiveness assessment**, which broadly impact patient outcomes and health economics. Finally, technological integration and novel insight generation have been made possible by progress in advanced data analytics and digital health technologies, emerging areas in which clinical translational pharmacologists have played a major role to date in collaboration with data scientists and engineers.

The Evolution to Clinical Translational Pharmacology

The broad range of subspecialties that clinical pharmacologists are involved in has evolved, and as noted above, it can be most useful to consider what clinical pharmacologists "did", exploring how these activities have changed and expanded over time into the current clinical translational pharmacologist.

The first generation of clinical pharmacologists were primarily medically trained physician-scientists whose training took place in an era largely absent of subspecialties. Subspecialty growth in the past was driven by advances in the scientific understanding of therapeutic pharmacology, dosing and drug disposition, and most clinical pharmacologists were physicians who acquired research training in a fellowship program. With the discovery and definition of pharmacokinetics and drug metabolism, scientists in Schools of Pharmacy began to play a greater role in the field, with training typically either through a post BS pharmacy PhD program (often in pharmaceutics) or a post-PharmD fellowship program. This has continued to the present day, though the post-PharmD fellowship has been largely replaced by clinical pharmaceutical science PhD programs. Later, as mathematical frameworks were developed to characterize the processes of absorption, distribution, metabolism and elimination of drugs, the disciplines involved in research in the field were broadened further. These increasingly sophisticated approaches to modeling drugs provided an invitation to other academic fields to enter the arena of clinical translational pharmacology, including those trained in engineering, mathematics, and statistics to apply their quantitative tools to pharmacology. The field of pharmacogenetics evolved along similar timelines, with technologies emerging in the 1980s and advances in genotyping and sequencing technologies facilitated by the Human Genome Project leading to rapid growth of the field in the 2000s. Most scientists working in pharmacogenetics in the early period came from clinical translational pharmacology backgrounds, acquiring the requisite knowledge and skills in genetics, genomics, and molecular biology, and even today most maintain a strong background in clinical translational pharmacology.

Thus, at present, clinical translational pharmacologists are comprised of physicians (with or without a PhD), pharmacists (either with a PharmD or PhD or both), or scientists coming from non-pharmacy or medicine backgrounds but with PhD training in clinical translational pharmacology/clinical pharmaceutical sciences. The challenge for those who come from a non-medical or non-pharmacy background is to complement their area of training with an understanding of drugs, pharmacology, physiology and disease pathophysiology, and it is not uncommon to see persistent gaps in the training. *Vice versa*, challenges do exist regarding the understanding and acceptance of model-informed approaches by data-driven clinical scientists.

Over the past decade, further scientific and technological advancements have changed and are continuing to change the scope and application of clinical translational pharmacology including the expansion from small molecules to a variety of novel modalities that interact with the biological system in more complex ways (such as complex biologics and cell and gene therapy), an evolution toward precision medicine methodologies and approaches (including more complex biomarkers approaches), advances in computational approaches and frameworks with greater application of data science, AI/ML approaches, and mechanistic modeling, a growing appreciation for the need to consider diversity and patient-centered approaches to drug development, and the introduction of new clinical trial paradigms including frameworks such as decentralization and adaptive trial designs. Taken together, these changes have resulted in a field characterized by fewer physician-scientists with a clinical translational pharmacology focus, more quantitative and data scientists driving PK/PD and QSP approaches, and changes in the translational science realm due to advances in complex biomarkers, “omics” approaches and a greater diversity of therapeutic approaches.

Emerging Trends in Science and Technology

Drug DDRU is a multidimensional challenge. Remarkable scientific, technological, policy, and infrastructural advances as well as societal and scientific community evolution have occurred in the past few decades that have had an impact across the DDRU spectrum. Given the exponential pace of discovery today, there are numerous emerging trends enabled by new tools, technology, and discoveries that are likely to shape the next decade of clinical translational pharmacology. Some emerging trends and their drivers are highlighted in the table below:

Translational Science, Biomarkers & Precision Medicine

Translational science and biomarker advances

- A one directional 'bench-to-bedside' approach is increasingly recognized as limiting. **Research starts with and returns to the patient**, acknowledging a powerful trend in research and medicine focusing on **patient-centricity** and **reverse translation**.
- **Reverse translation** activities aim to explain disease and patient biology through an integrative, cross-functional approach linking "omic" data derived from a deep characterization of patients with their health phenotype data. This has also led to identification of new "druggable" targets and development of novel therapeutics.
- Advances in genomics and other -omics (e.g., proteomics, metabolomics), imaging and bioinformatics capabilities have enabled the **identification of biomarkers** that are of diagnostic, prognostic, predictive, and monitoring nature.
- Innovations such as multiplexed assays can measure **multicomponent biomarkers** from a single sample. This combined with informatic capability to **integrate data** from various sources to perform multidimensional analysis and utilize methods like machine learning algorithms to interpret the complex data sets are driving biomarker utilization.
- Increased attention is being paid to ensure **standardization and validation** of assays and standardization of data collection and description as well as importantly, to understanding the **clinical utility** of findings.
- Patient-derived organoids allow for patient-specific ex vivo testing of drug responses and may be particularly valuable for the development of personalized medicines. **Microphysiological systems or 'organs-on-chips'** may be used to understand safety and drug metabolism.
- Advances in M&S (including mechanistic modeling) aid in translating in vitro study results and biomarker insights to inform drug development decisions.

Increase in the Development, Approval, and Utilization of Precision Medicines

- Advances in translational science and biomarker tools as well as utilization of quantitative approaches have led to advances in the development and utilization of precision medicines.
- Advances in analytical technology and informatic capability have helped combine different data sources to enable:
  - Fine-tuning **disease classification** utilizing biomarkers (e.g., EGFR+ NSCLC, SOD1 ALS)
  - Increase in development and approval of **targeted therapies** including **tissue agnostic** drugs
  - **Personalization of drug utilization** via labeling recommendations that (contra)indicate, select patients, modify dosage, allow for monitoring, etc. a drug in patient based on biomarker(s)
  - Development and utilization of **companion diagnostics**
  - Development and application of **clinical guidelines** (e.g., CPIC, DPWG) that provide drug-gene specific recommendations

Emergence of Novel Therapeutic Modalities

- Aided by a better understanding of disease biology, drug development is at an inflection point with many mature/established, advancing, and emerging therapeutic modalities being developed simultaneously.
- **Novel modalities** such as oligonucleotide therapeutics (ONTs including ASOs, siRNAs), other RNA therapies (e.g., mRNA vaccines), cell therapy (e.g., CAR-T), gene therapy (e.g., CRISPR), complex biologics (e.g., ADCs, bispecifics) as well as digital therapeutics are increasingly developed with ~4,000 clinical trials of new modalities (92% at the early stage) ongoing.
- Clinical translational pharmacology is **routinely applied** during development of established modalities (e.g., small molecules, monoclonal antibodies) and is **increasingly utilized** during the

development of some of the advanced novel therapeutics (e.g., ADCs, ONTs) and the extrapolation of existing treatments into the global health setting.

Clinical Research

Power of Patient-Centered Approaches

- Patient-centric clinical translational pharmacology improves patient outcomes and drives personalized healthcare:
  - While **patient-reported outcomes (PROs)** are sporadically/opportunistically utilized, a need for a systematic approach to integrate patient preference into drug development and approval has been recognized.
  - Since the start of COVID-19, there has been an increased incorporation of patient-centric approaches in clinical trial design such as using **decentralized clinical trial** (DCT) approaches and **digital health technology** (DHT).
  - There is an increased emphasis on data standardization and validation/qualification of tools.

Improving Health Equity

- Certain populations (e.g., pregnant or lactating women, and other specific populations) and certain diseases (e.g., rare diseases and neglected tropical diseases) are not studied sufficiently. However, there is recognition that incorporation of clinical translational pharmacology innovations can aid in considering **health equity and patient-centricity** at every stage of drug development, regulation, and utilization.
- Because **clinical translational pharmacology principles and tools** can enable understanding of drug disposition and exposure-response, it is increasingly possible to provide therapeutic recommendations for diverse (e.g., based on race, ethnicity, age, sex/gender, pregnancy status, lactation status, geography) patient populations.
- Additionally, increased adoption of **digital health tools** such as wearables, decentralized clinical trials, and telemedicine can help reach and retain underrepresented populations in clinical studies
- To promote **global health equity** and access to life-saving medicines, there is a focus on LMIC inclusive global clinical trials, collaborative funding partnerships, data sharing, and strengthening local research capacity. Global availability of generic drugs and biosimilars have increased because of advances in science (e.g., bioanalytical techniques, M&S approaches) and policy.

Rare diseases

- **Nearly half of the new drugs** approved in the past few years have been for rare diseases, many of which are **targeted therapies**.
- Drugs to treat **ultra-rare diseases as well as n-of-1/bespoke therapeutics** have also been developed and approved.
- There is still a **substantial unmet need** as most of the >7,000 rare diseases do not have an approved therapeutic.
- **Regulatory incentives and flexibilities** continue to drive development of drugs for orphan indications.
- There is a **role for clinical translational pharmacology** to play a key role in target selection, endpoint development, dose optimization and therapeutic individualization, and in generating evidence of effectiveness in studied and unstudied or understudied rare subsets.

Dose optimization

- Though dose selection and dose optimization are multidimensional problems, finding an **appropriate dose for the general population and optimizing the dose for an individual is a key role that clinical translational pharmacology plays**.

- In recent years, there is an increasing focus on adequate dose finding studies to refine/optimize dosing in late-stage trials (e.g., Project Optimus for oncology drugs).
- There is an increasing recognition that a **totality of data** (including PK, PD, and PGx data from preclinical, clinical, and modeling) need to be used to inform dose selection and optimization
- To optimize outcomes for an individual, **personalized/precision/n-of-1** dosing strategies may be needed based on patient-specific **intrinsic or extrinsic factors** such as age, weight, sex/gender, genetics, organ function, disease state utilizing **model-informed precision dosing approaches**.

New drug development and clinical trial paradigms

- COVID-19 brought with it unprecedented opportunities for innovation in ways that were not conceived or implemented to scale before. This means that clinical pharmacologists need to get comfortable in becoming multi-lingual scientists who can bridge the gap between various disciplines and collaborate in ways not done before. Some recent trends include:
    - Utilization of **adaptive trials** (including **Bayesian approaches)** has offered an increased flexibility in clinical trial design allowing for changes in inclusion/exclusion criteria (based on e.g., safety, efficacy, PD, biomarker) or study size. Real-time (interim) analysis of clinical trial data (e.g., response, PK, genomics) using M&S allows trials to adapt to the emerging data.
    - Utilization of basket trials, umbrella trials, and platform trials that collectively use **master protocols** to study several drugs or diseases in oncology and rare disease drug development.
    - Hybrid clinical trials with **decentralized components** and fully **decentralized clinical trials** that allow for electronic consent, in-home sample and data collection, remote patient monitoring, televisits, etc. have increased flexibility for individuals to participate and remain in clinical trials thereby increasing patient access and diversity.
    - **Patient-centric sampling (PCS)** focuses on making sample collection (e.g., dried blood spots, capillary blood collection, saliva, and urine collection at home) easier and less invasive.
    - Use of **digital health technologies** allows for real-time sample collection to enhance our understanding of safety events (e.g., correlation of biomarker to response).
    - Increasing focus on utilizing **real world data (RWD)** to develop real world evidence (RWE) to address post-marketing studies (e.g., Sentinel System) and to develop a synthetic control arm for rare diseases. From a clinical translational pharmacology perspective, RWD may be increasingly utilized to **identify potential DDI** in the real-world drug combinations used, identify safety events not observed during drug development (e.g., mediated by genetics), **optimizing dose** for patient subpopulations based on **baseline characteristics not routinely studied** in clinical trials.

Quantitative Medicine

Model-informed drug discovery and development

- Quantitative medicine approaches that utilize statistical, mathematical, or computational methods are **increasingly applied** to enhance activities and decision-making **across the DDRU spectrum**.
- Quantitative medicine approaches have been:
    - **Aiding development of precision medicines** including which therapeutic modality and drug candidate to pursue, support identification of appropriate biomarkers and patient subsets to pursue
    - **Aiding designing of clinical trials**, including simulation of clinical trials, understanding disease progression, prediction of safety profiles, informing inclusion/exclusion criteria, identification of dosing regimen.
    - **Enabling t**he use of **virtual/digital twin** approaches that can aid treatment decisions by simulating drug effects on individual patients and allowing for virtual experimentation of different test parameters (e.g., dosing regimen, timing, drug sequencing, disease progression)

while incorporating real-time patient data, in particular in the area of rare disease or for populations that are not easily studied.
  - **Informing patient care,** including improving diagnosis, and optimization of therapeutic strategy by identifying sequence/combination of therapies to utilize

AI/ML

- Advances in **computational approaches, data science, and application of AI/ML** approaches are providing unprecedented system-wide transformational opportunities to impact the entire DDRU spectrum by accelerating drug discovery through compound optimization, as well as biomarker discovery, streamlining drug development programs (e.g., designing trials, predicting safety and efficacy), aiding regulatory approval, and improving patient outcomes.
- Through the use of **AI/ML techniques**, quantitative approaches allow **combining large volumes of structured and unstructured** in vitro, in vivo, and in silico datasets (e.g., genomics, biomarker, clinical trial data, EHR, wearable, other PROs) to obtain **quicker insights** that can aid in **real-time decision making** and facilitate individualized patient care.

Other Considerations

Regulatory adaptation and harmonization

- **Regulatory stimulatory mechanisms** (via programs such as accelerated approval, breakthrough designation etc. as well as orphan designation and priority vouchers) have helped bring drugs faster to patients with unmet need with an increased patient centricity.
- Particularly relevant are resources and avenues for scientific interactions that enable addressing complex drug development challenges via the use of quantitative approaches (e.g., **MIDD program**, **complex innovative trial designs** program) and **Drug Development Tool qualification pathway** (e.g., biomarker qualification)
- International regulatory agencies have fostered international collaborations to address global drug development challenges via avenues such as **ICH guidelines** through which clinical pharmacology guidelines (e.g., DDI, bioanalytical methods) have been developed and will continue to develop (e.g., MIDD). **Regulatory clusters** are avenues for regulatory discussions on specific topics among international regulators. Of note, increased collaborations of established regulatory agencies such as FDA and EMA with the newly formed African Medicines Agency (AMA) is also anticipated.

Societal and broader scientific community trends

- **Misinformation and lack of trust in expert opinion** has become an increasingly serious issue in medical and public health decision making.
- **Unprecedented cuts in biomedical research** may have a significant long-term impact beyond the severe acute impact
- Open science and **precompetitive collaboration** are a mode of scientific work with many benefits and increasing utility and a largely positive impact on the work of clinical translational pharmacology.
- In scientific publishing, **open access** is a trend that impacts reporting and consumption of scientific work.
- **Convergence in science** has gained increasing attention and is both powerful and compelling, with great potential for driving breakthrough innovation. Convergence facilitates new frameworks, which, in turn, are expected to drive scientific discovery and innovation.

Opportunities and Challenges for the Future

The field of clinical translational pharmacology is well-versed in adapting to and harnessing state-of-the-art science and discovery. At present, the emerging new technology and capabilities bring vast opportunities and critical challenges that undoubtedly will shape the future of our field. Figure 2 illustrates these opportunities and challenges as themes that encompass many emerging trends. These elements are not meant to be all-encompassing but rather serve to spark reflection and generate ideas in anticipation of active discussion at the upcoming Summit.

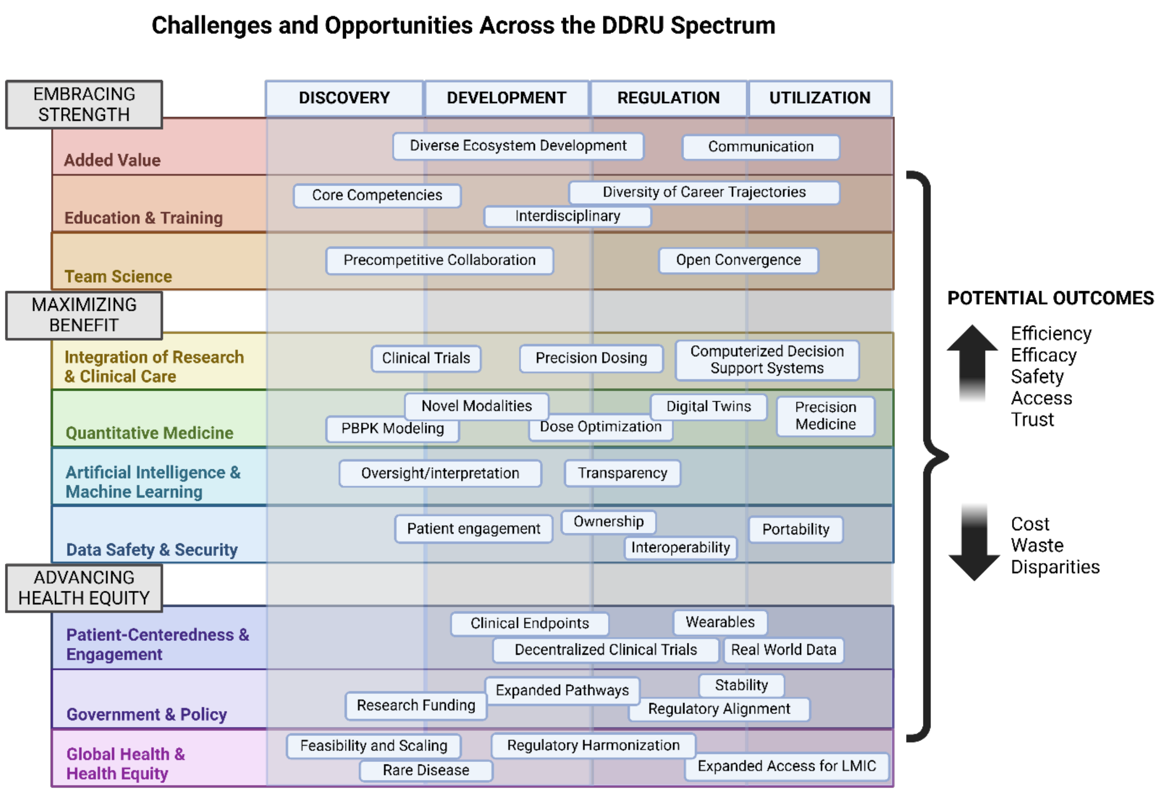

Figure 2. Challenges and opportunities for the future of Clinical translational pharmacology. Overarching themes are represented in each row with selected emerging trends embedded along the spectrum of discovery, development, regulation, and utilization (DDRU). Overcoming challenges and leveraging opportunities, many of which overlap, may yield potential outcomes (right) that improve drug treatment and human health.

Embracing the strength of our multidisciplinary nature through communication, training and collaboration.

Clear communication of the added value: We are a discipline of conveners and connectors, bringing together diverse perspectives and fostering collaboration, both instrumental in advancing team science and innovation. Clinical pharmacologists are inherently interdisciplinary, applying core pharmacology concepts to a variety of health and disease areas of interest. Many are ‘multilingual’ in science, able to translate field- or subspecialty-specific jargon for a broader audience and turn ideas into action with quantifiable impacts. One major challenge to the growth of the field is being able to effectively communicate the added value of the integration of these vital skills. What is the strength (and weakness) of our multidisciplinary nature and identity? How do we foster this integrator role and bridge building in a way that helps to maximize our value? How can we further strengthen and embrace our multidisciplinary nature while scientific and technology subdisciplines are expanding wider? And how can we bring in more scientists to embrace it and want to make it part of their own identity?

Misinformation and mistrust in expert opinion is an increasing headwind impeding the pace of innovation and advancement of human health. The scientific method and resulting evidence are in some cases ignored or directly attacked at the highest level with devastating consequences for public health. Given the multilingual and collaborative nature of clinical translational pharmacology, the field is ideally suited to fulfill the immense responsibility of educating the lay community how to consume and digest scientific evidence. An educated community will in turn serve as the best advocates for evidence-based policy. Combating misinformation and, in turn, promoting trust in science requires a specific skillset that can be learned. And we have an opportunity to develop a clear brand identity as an indispensable leader in educating society and clearly communicating the crucial role science and scientists play in ensuring the healthiest future. How can clinical translational pharmacology take on an explicit advocacy role for science and scientific progress?

Evolve education and training: Optimizing education and training for future clinical pharmacologists requires identification and prioritization of core scientific competencies in addition to ‘soft’ skills. The future likely requires interdisciplinary curricula (e.g., classic clinical pharmacology, biomarker science, quantitative medicine, data science/AI/ML, health equity), as well as experiential multi-sector learning, formal mentorship networks, and robust continuous education. With a long list of necessary skills, challenges exist in balancing breadth and depth and in keeping training programs nimble enough to react to rapidly evolving knowledge. What should be core competencies for clinical translational pharmacology? What mechanisms are needed to ensure comprehensive, interdisciplinary training programs? In addition, how could we enhance educational programs for non-clinical pharmacology disciplines, such translational science and engineering, to allow them to build sufficient insights into drug therapeutic action?

Foster team science: Team science accelerates innovation and discovery (e.g., Human Genome Project, COVID-19 Vaccine Consortia), enhances interdisciplinary collaboration (e.g. Critical Path Institute), and improves research efficiency through data sharing and shared goals (e.g. All of Us Research Program). Coordinated funding initiatives have successfully leveraged a team science approach to improve diversity and access for historically under-researched populations (e.g., Environmental influences on Child Health Outcomes (ECHO) study ensure diverse populations are included in research, enhancing equity). Opportunities exist to ensure clinical translational pharmacology is viewed as a clear leader in team science. How can clinical pharmacologists leverage unique skillset to resolve existing challenges (e.g., coordination complexity, resource distribution, data integration and interoperability, and sustained momentum through long-term funding and commitment)?

Maximizing benefit and safety for every patient

Integration of clinical care and research: To generate answers to complex questions related to health and disease, it is essential to integrate research within clinical care, seeing every patient as an opportunity to learn how to improve outcomes and deliver optimal care in the most cost-efficient way. Computerized decision support systems (CDSS) and model-informed precision dosing (MIPD) serve as success stories of integration and have demonstrated improved patient outcomes, enhanced safety and optimized treatment. CDSS and MIPD have been utilized across many clinical specialties (e.g., oncology, hematology, infectious diseases) with immense opportunity for expansion. Indeed, vast opportunities exist to deepen the integration of clinical care and research to demonstrate therapeutic and cost effectiveness and determine long-term treatment benefits vs. risks. Potential conduits for integration also present challenges and include innovative clinical trial paradigms, early collaboration with and adoption by stakeholders (e.g., healthcare systems, payers, patient advocacy groups), identification of meaningful patient-centered outcomes, and improved bioinformatics interoperability and interpretability. Indeed, clinical translational pharmacology has experience leveraging clinical data (e.g., Real-Word Evidence -RWE) to generate and test hypotheses, identify safety signals, and understand trends. Legislative requirements (e.g., HIPAA and 21st Century CURES act) have been an effective 'stick' (or carrot, if you hold a more optimistic view) to improve electronic health record portability and transparency necessary for the most informative datasets. How do we tap into the immense resource that clinical data present to support efficient drug development and repurposing efforts, understand optimal utilization patterns, and inform health equity initiatives?

Advance Quantitative Medicine: Quantitative medicine has revolutionized clinical translational pharmacology and has arguably established itself as a cornerstone of our field. Evidence of quantitative medicine is seen across the drug DDRU spectrum from fast-fail initiatives and biomarker integration that strive to expedite drug development through a model-informed development paradigm. Clinical translational pharmacology has seen the advent of novel modalities that require new tools. Quantitative medicine has expanded and adapted to meet these needs, leveraging preclinical and in vitro evidence paired with clinical data to identify meaningful individual differences that impact drug selection, dosing, and response. While the number of biomarkers in development has risen substantially in the past decade, the future will likely see more multi-component biomarkers to gain precision and specificity in quantitative medicine. The advances in AI/ML and advanced statistical methods will need not only to be developed and deployed but also made digestible to the scientific and clinical communities. The virtual patient populations in quantitative systems pharmacology modeling may evolve into real time use of digital twins in clinical trials and at the patient bedside. While the future of quantitative medicine is limitless, how do we prioritize goals, improve access and uptake of clinically actionable models, increase acceptance, and reduce model bias towards certain populations?

Fully leverage Artificial Intelligence and Machine Learning (AI/ML): AI and ML hold much promise in transforming how we do science and are already integrated into daily workflows to improve efficiency in various settings and are essential for quantitative medicine. Computational and data science behind AI/ML are arguably becoming core competences for scientists and future leaders. If not deep knowledge of theory and processes, clinical pharmacologists of today and tomorrow likely require a working knowledge of basic concepts, advantages and limitations of various approaches, as well as ethical considerations such as privacy, transparency, accuracy, and access. Current AI/ML model performance demonstrates the importance of human content experts embedded to ensure the biological plausibility of ML paradigms, and review and verify AI generated output. For clinical translational pharmacology, what are best practices and field standards for ethical and equitable use?

Ensure Integrity of Data Sharing and Safety: As we move toward the standard expectation of open science and data sharing, balancing data sharing with safety is essential to ensure privacy, security, and ethical use while retaining patient trust. There are well described opportunities to enhance research productivity and collaboration through open-access databases, to expand diversity of datasets through inclusion of historically under-represented participants across the globe, and to leverage AI/ML to identify patterns not otherwise discernable on a smaller scale. What role do clinical pharmacologists have in ensuring data sharing and safety?

Advancing health equity and promoting global health

Foster Patient-Centeredness and Engagement: Successful patient engagement across the DDRU spectrum has become a transformative force in the pharmaceutical and healthcare industries. Best practices include incorporating patient insights in early-stage research to identify unmet needs and determine meaningful clinical endpoints, as well as inform clinical trial design and feasibility in the target population. Patient-generated data (e.g., wearables, health apps) can be accessed to provide a more holistic view of health and disease. RWE can be leveraged for pharmacoepidemiologic approaches when randomized controlled trials are not feasible or yet justified. Elevating patient advocates into advisory roles can be useful to define tolerable risks and inform risk-benefit assessments. Going forward, what opportunities exist for meaningful patient engagement across the DDRU spectrum?

Global harmonization of governance and policy: Over the past decades, significant regulatory and policy advancements have influenced clinical translational pharmacology. Key developments include expedited regulatory pathways (Fast Track, Breakthrough Therapy Designation), addressing unmet needs (e.g., Best Pharmaceuticals for Children Act), and global guidance (e.g., FDA and ICH guidance development regarding MIDD and RWE). Given the great extent that government and policy impact health and medicine, changes in the administrative priorities of large government make it challenging to create stability when science both benefits from and is hindered by such decisions (e.g., budget priorities and delays). Still significant differences exist between countries and regions in the speed of adoption of advanced methods in regulatory assessment that impact global harmonization. Creating nimble scientific entities and funding mechanisms able to adapt and respond to such sways is both a challenge and opportunity. How can this be accomplished across the sectors of clinical translational pharmacology (e.g., industry, academia, regulatory)?

Advance Global Health and Health Equity: There remain opportunities to create equitable partnerships through fair representation of low- and middle-income country (LMIC) researchers and stakeholders in global projects, to promote transparency and collaboration that accelerate discoveries relying on big data to benefit underserved populations, as well as incentivizing development of cost-effective, scalable solutions, particularly for those that provide access in underserved regions or populations. How can clinical translational pharmacology best impact global health and foster health equity worldwide?

Call to Action

The field of clinical translational pharmacology has grown over the past century with the advent of new sub-specialties, the expansion of engagement across the DDRU continuum, and the expansion of novel therapeutic modalities. While the population of clinical pharmacologists may look less and less homogenous with the growth of specialties in quantitative medicine, translational science, pharmacogenomics, real word data, and more, what is more true than ever is that the clinical pharmacologist, as an integrated drug developer, is critical to achieving the unchanged goal of developing, selecting, and providing the right drug at the right dose and at the right time for the right patient, and for all patients.

Gathering leaders from the many sectors of clinical translational pharmacology at this **Summit on the Future of Clinical Translational Pharmacology** is an exciting opportunity to envision what the future may look like. In particular, the focus is around the question: **Leaving no patient behind: how can clinical translational pharmacology seize the opportunity to maximize benefit and safety for every patient, advance health equity, and promote global health?** However, participation in the summit also comes with the responsibility of working together to create that future by articulating what needs to occur in the next decade.

As participants in this Summit, the ask of you is both simple and ambitious. First, engage in discussion with the sense of urgency that mirrors that of the patients who are waiting for a therapy that may change the course of their disease. Second, think big about what a future could look like where clinical translational pharmacology is even more impactful than it is today in bringing therapeutics through the DDRU continuum more quickly, with higher success rates, and with greater equity, and across all geographies. Third, consider what needs to evolve to enable that future? What changes or novel frameworks should be considered for training programs, collaborations and partnerships, or innovations in science (and uptake of this innovation)? Additionally, what are pragmatic road maps to help move from the present state to that desired future? Finally, what commitment can you make to help us achieve that future?

Further Reading

Selected references for further in-depth reading are provided here.

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ASCPT Summit Task Force

Matthew Rizk, PhD, ASCPT President, Chair
Sandra Visser, PhD, ASCPT President-Elect, Co-Chair
Julie Johnson, PharmD
Anu Ramamoorthy, PhD
Stephani Stancil, PhD, APRN
John Wagner, PhD
Issam Zineh, MPH, PharmD

ASCPT Staff
Abigail W. Gorman, MBA
Megan McBeath Hay

American Society for Clinical Pharmacology & Therapeutics