Institution: The University of Manchester		
Unit of Assessment: 3 (Allied Health Professions, Dentistry, Nursing and Pharmacy)		
Title of case study: Modernising Drug Development Practices for Precision Dosing in Diverse Patient Populations		
Period when the underpinning research was undertaken: January 2007 - February 2017		
Details of staff conducting the underpinning research from the submitting unit:		
Name:	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Amin Rostami-Hodjegan	Professor of Systems Pharmacology	2009 - present
Leon Aarons	Professor of Pharmacometrics	2004 - present
Aleksandra Galetin	Professor of Translational Pharmacokinetics Reader Senior Lecturer Lecturer	2020 - present 2016 - 2020 2011 - 2016 2004 - 2011
Jill Barber	Reader	2004 - present
Kayode Ogungbenro	Senior Lecturer Lecturer in Cancer Pharmacometrics Research Fellow	2020 - present 2014 - 2020 2005 - 2014
Adam Darwich	Lecturer in Model-Based Individual Dosing Research Associate	2016 - 2019 2013 - 2016
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Traditional drug development leads to drug doses that are sub-optimal for >40% of patients, thereby increasing the risk of adverse effects and/or reducing efficacy. This highlights the need to tailor the dose to the individual. The Centre for Applied Pharmacokinetic Research (CAPKR) at the University of Manchester (UoM) has demonstrated significant inter-individual variations in the level of drug-handling proteins. Physiologically-based pharmacokinetic (PBPK) modelling utilised by CAPKR has changed practice in drug development. PBPK is now:

- adopted by the global pharmaceutical industry,
- part of filing for drug approval to world leading regulatory agencies: (USA, Food and Drug Administration (FDA); Europe, European Medicines Agency (EMA); UK, Medicines and Healthcare products Regulatory Agency (MHRA); and Japan, Pharmaceuticals and Medical Devices Agency),
- formally regulated by inclusion in FDA/EMA/MHRA guidance for industry.

These processes are now facilitating individualized drug dosing.

2. Underpinning research

Individualised dosing (the right dose for the right patient at the right time) is crucial for the most efficacious use of medications while minimising the risk of harm. The drug development process has traditionally focused on a 'one-size-fits-all' dose, based on a narrow subset of patients who may not be representative of the patient eventually receiving the drug in the real world. Over the last seven years members of CAPKR (Rostami-Hodjegan, Aarons, Galetin, Barber, Ogungbenro and Darwich) alongside many top scientists from industry, academia and regulatory agencies, through professional bodies such as the American College of Clinical

Pharmacology, indicated their concerns over the inadequacy of strategies for dose adjustment in special populations. Applications of PBPK modelling in CAPKR have demonstrated a range of opportunities to fill the gaps in stratified dosing [1].
These changes were achieved by integrating *in vitro* data on drugs with the knowledge of the systems biology and physiology (e.g. [2] in health and disease). This approach has paved the way for combining various pieces of information on each different subset of patients with the aim of predicting the optimal dose in the absence of any clinical data [3].

The research conducted at the UoM relevant to the impact can be summarised in three categories:

(i) Establishment of drug-independent physiological and pathophysiological systems attributes such as the abundance and activity of drug metabolising enzymes and transporters and their temporal changes in special patient populations, and identification of translational scaling factors based on microsomal and cytosolic protein measurements in various human tissues (e.g., liver, intestine, brain and kidney) [2, 4]. This allows quantitative translation of *in vitro* metabolism and transporter kinetic data into *in vivo* consequences.

(ii) Creation of mechanistic modelling frameworks for such translation e.g., extrapolation methodology for gut wall permeability, transporter-mediated disposition in kidney (particularly in patients with renal impairment), assessment of metabolism-transporter interplay in liver and corresponding drug-drug interactions (DDI) [3, 5]. Complementary use of the clinical data and combining the so-called 'bottom-up' and 'top-down' modelling has been advocated by CAPKR [3].

(iii) Demonstration of translational modelling applications beyond typical healthy individuals to facilitate precision dosing [6]. The specific patient sub-groups where CAPKR had produced *direct* and *unique* evidence for feasibility of PBPK is described in a variety of research articles and summarised in [6]. They include (but are not restricted to) neonates and young children, pregnant women, obese patients particularly those undergoing bariatric surgery and patients with chronic kidney disease.

All of the above underpins the role of CAPKR in increased application of PBPK modelling for drug label statements (14 cases in 2019 alone; >60% of all approvals).

3. References to the research

1. **Rostami-Hodjegan, A**. Physiologically based pharmacokinetics joined with in vitro-in vivo extrapolation of ADME: a marriage under the arch of systems pharmacology. *Clin Pharmacol Ther* 2012; 92, 50-61 (2012). doi:10.1038/clpt.2012.65.
2. Abduljalil, K., Furness, P., Johnson, T. N., **Rostami-Hodjegan, A**. & Soltani, H. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. *Clin Pharmacokinet* 2012; 51, 365-396. doi:10.2165/11597440-000000000-00000.
3. Tsamandouras, N., **Rostami-Hodjegan, A**. & **Aarons, L**. Combining the 'bottom up' and 'top down' approaches in pharmacokinetic modeling: fitting PBPK models to observed clinical data. *Br. J. Clin. Pharmacol.*2015; 79, 48-55. doi:10.1111/bcp.12234.
4. Achour, B., Russell, M.R., **Barber, J.** & **Rostami-Hodjegan, A.** Simultaneous Quantification of the Abundance of Several Cytochrome P450 and Uridine 5'-Diphospho-Glucuronosyltransferase Enzymes in Human Liver Microsomes Using Multiplexed Targeted Proteomics. *Drug Metab Dispos* 2014;42, 500-510. doi:10.1124/dmd.113.055632.
5. Zamek-Gliszczynski MJ, Lee CA, Poirier A, Bentz J, Chu X, Ishikawa T, Jamei M, Kalvass JC, Nagar S, Pang KS, Korzekwa K, Swaan PW, Taub ME, Zhao P and **Galetin A.** ITC Recommendations on Transporter Kinetic Parameter Estimation and Translational

Modeling of Transport-Mediated PK and DDIs in Humans. *Clin Pharmacol Ther* 2013; 94, 64-79. doi: 10.1038/clpt.2013.45.

6. **Darwich, A.S**., **Ogungbenro, K**., Vinks, A.A., Powell, J.R, Reny, J-L., Marsousi, N., Daali, Y., Fairman, D., Cook, J., Lesko, L.J., McCune, J.S., Knibbe, C.A.J., de Wildt, S.N., Leeder, J.S., Neely, M., Zuppa, A.F., Vicini, P., **Aarons, L**., Johnson, T.N., Boiani, J. & **Rostami-Hodjegan, A**. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. *Clin Pharmacol Ther* 2017; 101, 646-656. doi:10.1002/cpt.659.

4. Details of the impact

Context

Our research at the UoM has made a significant, direct and global impact in shifting the paradigm of drug development away from 'one-size-fits-all' dosing strategies. CAPKR research has enabled exploration of new avenues to address dosage regimen requirements for special populations by integrating information regarding the system attributes (abundance of enzymes/transporters) into PBPK predictive models. In the words of the Deputy Director of the FDA Office of Clinical Pharmacology (OCP):

"*The CAPKR group has published several seminal pieces of novel research related to 'stratified medicine' particularly in paediatrics, pregnant women and obese patients undergoing bariatric surgery which have been very informative and led to actionable changes in drug development and patient care*." [Ai].

CAPKR has also delivered economic and ethical benefits via reducing the number of clinical studies. The testimonial by the Vice-President and Global Head of Clinical Pharmacology at Pfizer states:

"We typically conducted 25 to 40 or more clinical pharmacology studies to evaluate all these potential intrinsic and extrinsic factors for each new medicine before requesting regulatory approval. These studies add to the cost and time of developing new medicine and contribute to the escalating cost of new medicines for patients and tax payers around the world. We (now) *make extensive use of PBPK models to inform our strategy about the necessity to conduct or avoid particular clinical pharmacology studies*." [Bi].

Pathways to impact involved

- A close collaboration with the FDA (under a Memorandum of Understanding Agreement signed by the Director of Center for Drug Evaluation and Research, FDA [C]), which has helped us translate the latest Drug Metabolism and Pharmacokinetics (DMPK) science into practice under the Model-Informed Drug Development (MIDD) approach.
- Regular site visits, and sabbatical stays at the FDA (Galetin and Rostami).
- Contributions as key opinion leaders in EMA/ FDA internal workshops/discussion panels (Aarons, Galetin, Ogungbenro and Rostami).
- Direct engagement with the senior leadership of Clinical Pharmacology and DMPK operations of pharmaceutical companies [Bi-Bv].
- Practical Pharma interaction via CAPKR membership to carry out pre-competitive research (up to GBP100,000 per annum per member), and currently includes companies Eli Lilly, GSK, AbbVie, Merck-Serono, Janssen, Merck-Sharp & Dohme, Genentech and Takeda.

Reach and significance of the impact

CAPKR's translational modelling has been widely adopted by pharmaceutical companies and regulatory agencies. The impact can be viewed as follows:

1. Individualized dosing. The 'one-size-fits-all' approach in drug development does not consider that individual responses of patients can vary significantly as a result of

physiological/biological differences which stem from genetics, environment, ethnicity or age. Recognizing this challenge and to address these issues, the FDA held a workshop in August 2019 on 'Precision Dosing', a term first coined by CAPKR in 2016. From this the FDA released new guidance (November 2020) entitled '*Enhancing the Diversity of Clinical Trial Populations*' [D]. The guidance acknowledges that in traditional drug development certain populations are often excluded from trials without strong clinical / scientific rationale (e.g. individuals with organ dysfunction). It also indicates that failure to include participants with complex comorbidities in a development program may lead to a failure to discover important safety information.

Global health advocates (Gates Foundation) have also been a beneficiary of our research findings. The research has created the opportunity for developing new rational guidance for drug treatment in orphan disease groups such as pregnant patients in developing countries which are not studied as part of clinical drug development [E].

2. Modernising drug development and changing regulatory perspective. Using PBPK modelling, CAPKR have shown how to evaluate and include individualized factors into a dosage regimen prior to conducting any clinical studies. Many PBPK predictive models are now implemented in commercial software [F] and incorporated into drug development practice within the pharmaceutical industry, encouraged by global regulators. The FDA position paper regarding disparity of the impact of DDI and genetic polymorphism in paediatrics vs. adults [Gi] is based directly on CAPKR's research on variable ontogeny of drug metabolising enzymes and transporters. Furthermore, 2020 FDA Guidance for patients with renal impairment [Gii] considers the use of PBPK modelling for dose adjustment guidance which also links to CAPKR's translational modelling in this patient cohort.

The implementation of these approaches as part of MIDD to inform new drug labels necessitated building confidence at a level where regulatory bodies could accept PBPK models in lieu of clinical studies. Between 2008-2017, nearly 100 new drug applications containing PBPK analyses were submitted to the FDA OCP and the drug label for 70 of the approved cases had statements based on PBPK. The role of CAPKR in industrialising PBPK applications is indicated by testimonials from regulatory agencies [Ai], [Aii] and top leadership within global pharmaceutical companies [Bi-v], e.g. Head of Quantitative Pharmacology & Pharmacometrics and Vice President, Merck:

"CAPKR has an outstanding research record and pioneered innovative scientific approaches that have greatly impacted the methodologies for scientific approaches and review recommendations". [Bii].

CAPKR research had a *'direct'* impact on adoption of new regulatory practices and development of official guidance documents dealing with PBPK models [Hi], [Hii], indicated by the testimonial from the Pharmacokinetic Group Lead of the MHRA:

"…*they* (CAPKR) *have been influential in leading the outcomes (bottom-up and top-down modelling) which all ultimately contribute to some policy changes and regulatory guida*nce". [Aii].

5. Sources to corroborate the impact

A. Testimonials confirming that the work of CAPKR led to changes in policy, regulatory guidance, drug development and patient care.
   i. The Deputy Director of the Office of Clinical Pharmacology, FDA (dated 14 February 2018).
   ii. The Pharmacokinetics Group Lead of the MHRA (dated 17 October 2019).

B. Testimonials from the pharmaceutical industry leadership, confirming the impact that CAPKR has had on dose adjustment for special populations
   i. Pfizer (Groton, USA), Vice President and Global Head of Clinical Pharmacology (dated 18 May 2017).

ii. Merck (Philadelphia, USA), Head of Quantitative Pharmacology & Pharmacometrics (dated 12 June 2017).

iii. Roche (Basel, Switzerland), Global Head of Clinical Pharmacology (dated 21 February 2018).

iv. Astellas (Chicago, USA), Global Head of Pharmacokinetics and Modeling & Simulation (dated 31 March 2018).

v. Merck (Darmstadt, Germany) Global Head of Pharmacology and Drug Disposition (dated 7 June 2017).

C. Memorandum of Understanding Agreement (dated 21 April 2015) between the UoM and the US FDA, evidencing the unique relationship between CAPKR and the FDA facilitating the path to impact.

D. FDA Position (dated November 2020) on precision dosing and clinical trial recruitment, indicating the direct role of CAPKR in shifting policies towards 'unacceptability' of one-size-fit-all paradigm in drug development.

E. Testimonial letter (dated 23 October 2019) on global health impact from the Senior Policy Officer at the Bill & Melinda Gates Foundation, confirming the importance of CAPKR's work in ensuring that special populations, such as pregnant women, are included in drug development studies, with the potential for being rolled out in the 3rd world.

F. Testimonial letter (dated 1 November 2019) from the President and Managing Director of Certara UK Ltd, confirming the impact that CAPKR has had on the uptake, recognition, and subsequent growth of PBPK modelling platforms within the global pharmaceutical industry and regulatory sciences arena.

G. Example of FDA guidelines and perspectives on the special populations with direct applications of PBPK. These back up the role of CAPKR in changing opinion regarding application of PBPK in special populations, enabling the inclusion of patients with renal impairment and young paediatrics.

i. FDA position paper from 2018 on the disparity of the impact of DDI and genetic polymorphism in paediatrics versus adults.

ii. FDA Guidance from 2020 for drug dosing in patients with renal impairment.

H. EMA and FDA official PBPK guidance on how to apply the approach during drug development and filing for regulatory approval, confirming the adoption of the PBPK modelling approach in drug development and its necessity for regulatory approval.

i. EMA Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (dated 21 July 2016).

ii. FDA Physiologically Based Pharmacokinetic Analyses - Format and Content. Guidance for Industry (dated December 2016).