Patient Focused Target Product Profiles (TPPs) for Cystic Fibrosis (CF) Related Infections

Virtual Symposium Meeting Report

CATAPULT Medicines Discovery

Cystic Fibrosis Trust

Contents

Executive Summary

The Cystic Fibrosis (CF) Syndicate in Antimicrobial Resistance (AMR) is a partnership between Medicines Discovery Catapult and the Cystic Fibrosis Trust. It brings together the CF community with a vision to accelerate the development of antimicrobial treatments for CF, bringing new effective treatments to people with CF, faster.

To guide and catalyse CF antimicrobial development, the CF Syndicate in AMR has developed patient-focused TPPs for CF-related infections. The TPPs have been built around the needs and priorities of people with CF and reinforced by clinical and industry insight and expertise. A Virtual Symposium was convened on April 30 2021, bringing people with CF together with leading experts from academia, industry and the clinic. The Symposium facilitated feedback and discussion on the Patient-Focused TPPs for CF-Related Infections, to help shape and finalise them as useful tools for the community.

The Virtual Symposium highlighted key gaps and challenges that should be reflected in the TPPs and could be addressed through a collaborative approach in order to speed the development of new CF antimicrobials and their translation to the clinic:

1. A better understanding of CF pulmonary exacerbation pathophysiology
2. The development of diagnostic and predictive biomarkers of new infections and pulmonary exacerbations, and for ongoing monitoring of treatment efficacy
3. The creation of new patient reported outcome tools and digital apps to enable self-reporting, including the ability to link data to patient registries to enable longitudinal analyses
4. The development of new drug delivery devices and reformulations for more efficient and less burdensome treatment regimes
5. The identification of novel drug combinations e.g., antimicrobial synergy with biofilm disruptors and mucolytics

The CF Syndicate in AMR will continue to bring the community together to scope these areas, identify ongoing research and drive impactful collaborations to fill gaps and address areas of patient and clinical need.

1 | Patient Needs and Priorities for New CF Antimicrobial Treatments

At the Virtual Symposium, Luke Twentyman spoke about his experiences as a person who has lived with CF for 49 years. Luke flagged three specific themes for consideration when discussing the development of new CF antimicrobial treatments:

1. Burden of healthcare
2. Quality of life
3. Stability of health

People with CF experience a huge **burden of healthcare**, from taking dozens of oral tablets a day and sometimes nebulized treatments, often at set times and in a certain order, to carrying out physiotherapy for several hours per day, whilst also balancing eating, exercising, resting and sleeping.

After taking these treatments, people with CF are also burdened with cleaning and sterilizing nebulisers after each use, maintaining drug stocks, ordering and collecting medicines, scheduling and attending hospital appointments, whilst living everyday with the worry of their next in-patient stay lurking around the corner.

Even when people with CF adhere to their medications, they can face unpleasant adverse effects meaning additional medicines are required to counteract them. The combination of all of these factors can have a huge impact on the overall outlook and **quality of life** of people with CF as a whole.

The ability to plan ahead and look optimistically towards the future is unfortunately not granted to every person with CF. However, as new treatments are developed, it is hoped that people with CF will develop a **greater stability** in their lives.

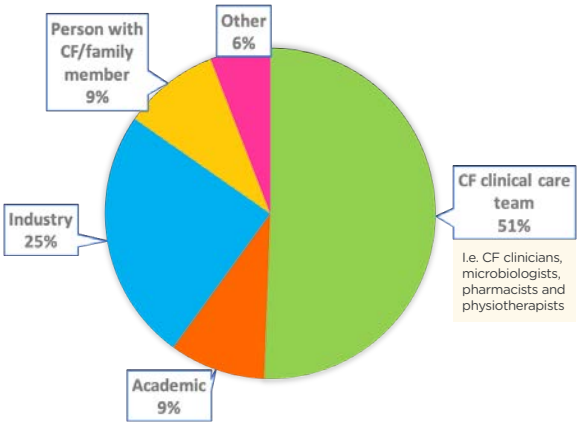
The TPPs provide a roadmap to enable the development of new medicines that will see the burden of care reduced, stability of life increased and ultimately the overall quality of life for all those with CF.

2 | TPP Development Process

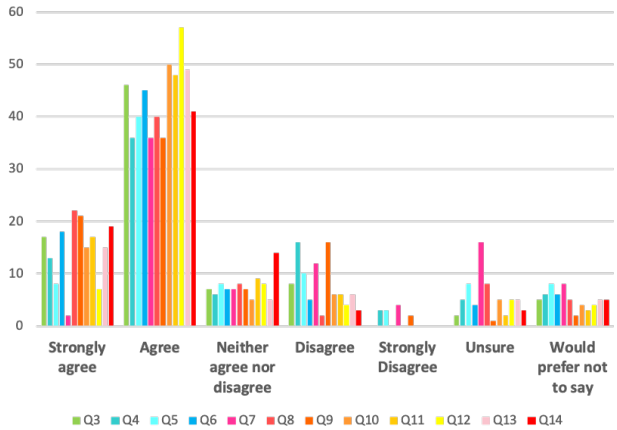
Jessica Lee from Medicines Discovery Catapult described how the CF Syndicate in AMR has taken an innovative patient-focused approach to develop TPPs for CF-related infections. The process began with a focus group involving people with CF and their carers; this enabled the identification of their unmet needs and priorities. One area that came across strongly in the focus groups was the **burden of care** that is faced by people with CF, as outlined by Luke Twentyman above, this forms a core of the TPPs. These insights of people with CF were then reinforced with clinical and industry expertise gained through focused engagement activities.

To gain initial feedback on the TPPs, a Delphi survey was conducted and received 85 responses internationally across a range of respondent types. Overall, the Delphi survey demonstrated that there was a good consensus from the community across the TPPs, with the majority of respondents agreeing or strongly agreeing to most questions asked.

85 Respondents



Consensus across the TPPs



The areas of the TPPs that were identified through the Delphi survey as having less consensus on within the community were:

- The treatment durations suggested for new therapeutics
- The use of CF animal models and traditional infection rodent models in preclinical studies
- The use of patient reported outcomes (PROs) as primary clinical trial endpoints in clinical studies

These areas were discussed in detail at the TPP Virtual Symposium to enable leaders in the field to interact with people with CF and other stakeholders to identify the challenges and opportunities faced in addressing these topics.

3 | Duration of CF Antimicrobial Treatment

Current state of play

- Due to their duration and side effects, some antimicrobial treatments are **very challenging for people with CF to adhere to**, for example, it's not uncommon for people with CF not to finish a full course of eradication treatment for *Mycobacterium abscessus*.

- Questions around the efficacy of antibiotics and the duration of treatments has been motivated by remarkable findings by studies such as the Nix-TB trial[1], which demonstrated that given the right combination of treatments, **treatment duration can be shortened dramatically**.

- There is a **lack of evidence** to suggest how long current antibiotic treatments should be given for in CF. The STOP2 trial[2] is currently exploring treatment durations of IV antibiotics in people with CF.

- We currently have a **limited understanding of the biology of pulmonary exacerbations** and how to treat them. Currently, on the onset of an exacerbation, many clinicians will prescribe antibiotics without fully understanding the cause of the exacerbation and without first trying alternative treatments. This initial treatment with a potentially unnecessary antimicrobial could irreversibly affect the lung flora, and could mark the beginning of antimicrobial resistance in people with CF.

Needs and priorities of people with CF

- People with CF want to know that they are **not taking unnecessarily long treatments** of antibiotics. Evidence is currently being generated for existing treatments to identify the appropriate treatment durations, for example the STOP[2] study and to standardize diagnosis and treatment of *M.abscessus infections* (PATIENCE[3] and PREDICT[4] studies).

- People with CF would ideally like to never have an infection or go through eradication treatment in the first place, so should we place an increased focus on infection prevention and ***Pseudomonas aeruginosa* eradication**?

- Acceptance and adherence to new treatments by people with CF will be highly dependent on the likelihood of a positive outcome. If **ongoing monitoring** (e.g., serum monitoring using biomarkers?, patient reported outcomes through an app like Project Breathe[5], apps to transfer data on lung function or blood glucose data) could provide evidence to suggest a treatment is working, that would also likely improve adherence, especially to more challenging regimens.

  For example, treatment with aminoglycosides can result in hearing loss and/or tinnitus. As there is no way to predict response to a drug, it's difficult for people to make a decision on whether they should continue to take it.

[1]https://www.nejm.org/doi/full/10.1056/NEJMoa1901814
[2]https://www.cff.org/Trials/finder/details/455/STOP-2-Treatment-of-pulmonary-exacerbations-in-people-with-CF
[3]https://clinicaltrials.gov/ct2/show/NCT02419989
[4]https://www.cff.org/Trials/Finder/details/503/PREDICT-NTM-observational-study-
[5]https://www.cysticfibrosis.org.uk/what-is-cystic-fibrosis/cystic-fibrosis-care/personalised-healthcare/project-breathe-app-for-remote-health-monitoring

- The treatment durations that would be accepted by people with CF are determined by a number of factors including route of administration of the drug, whether it has to be taken at the hospital, side effects etc.

- It's important that clinicians **treat people with CF as disease experts** and appreciate that they can understand the full extent of their condition and treatments, so that they can make informed and shared decisions about which treatments they take.

Challenges

- Current microbiology **susceptibility testing does not predict clinical outcomes** so there is a question of how to translate lab diagnostics to give the best guidance to prescribers. Additional research for diagnostics to help us understand the complex microbiome is essential.

- Changes to current prescribing practices would require a **shift in culture and clinician mindset**; it's unlikely that the majority of prescribers would trigger an antimicrobial treatment based on a PCR test alone, for example, and would still require a positive culture result. This provides a potential barrier to enabling early treatment.

- Could shortening treatment times actually result in a shorter time to the next exacerbation and impact on antimicrobial resistance? **New studies are needed** to rule this out.

- Often, drugs that are prescribed off license in CF were **originally developed for other indications** so we don't know what dose and duration would be recommended for people in CF.

Opportunities

- The development of **new adjuvant therapies** (e.g., mucolytics, biofilm disruptors) that can be given in combination with currently prescribed antibiotics could potentially not only improve clinical outcomes but also reduce treatment duration.

- There's a huge opportunity for the development of **better biomarkers** to predict responses to treatment that better predicts clinical outcome, as well as **earlier validated endpoints** to enable treatment efficacy to be assessed at an earlier stage.

- The development of a **diagnostic to detect infections early** could be transformative to enable earlier treatment of infections, potentially even avoiding the use of antimicrobial therapies and instead substituting for high intensity physiotherapy, for example.

- Could there be a role for developing **preventative vaccines** for CF? Although there was disappointment for these approaches in the past, newer technologies have now been developed which could yield more success.

- Is it possible to **develop and validate preclinical models** that can better predict treatment duration requirements in people with CF?

- Could **new modalities such as phage treatment** which may be relatively safe and could require less frequent dosing and shorter treatment regimens, be promising new approaches for CF to reduce the burden of care?

- Opportunities to **end siloed working** and focus more on bringing together expertise and innovation in drug synergy, biofilm disruption and diagnostics to make treatments more effective over a shorter duration.

4 | Preclinical Models for CF Antimicrobial Development

Current state of play

- Current preclinical models in CF include:
  - CF animal models e.g. mouse, rat, ferret, pig and sheep. To our knowledge, none of these models reflect the chronic airway infection observed in people with CF and do not completely recapitulate other pathological features seen in humans such as the complex lung architecture, biofilms, mucus production and pH.
  - *In vivo* models of infection e.g., mouse thigh model or agar-bead pulmonary infection model, which may be relevant to? evaluate efficacy and safety of certain antimicrobials dependent on their mechanism and route of administration. In addition, the *Galleria mellonella* infection model is a good *in vivo* model for high throughput screening prior to evaluation in mammalian models.
  - *Ex vivo* models that are well established include the pig *ex vivo* lung model. *Ex vivo* models still being validated include whole sputum testing, patient-derived organoids and air liquid interface models, using patient cells.
- For traditional antibiotics, to show proof of concept that a drug is efficacious, more **traditional rodent infection models have been used successfully** to gain investment or regulatory approval, including the mouse thigh infection model. However, these models must be carefully selected so that they are relevant based on the therapeutic approach and route of administration.
- In most cases, investors and regulators still **require the use of animal models to demonstrate both efficacy and safety prior to advancement to human studies**, which can be a barrier for less traditional antimicrobial approaches.
- To our knowledge, **no current approved therapies for CF have used CF animal models** during preclinical development, e.g. Ivcaftor's EMA assessment report quotes: "*In vivo* pharmacodynamic studies were not performed due to lack of validated CF animal models. Therefore, an *in vitro* model comprising primary human bronchial epithelial (HBE) cells from CF patients was used[6]." However, ivacaftor was evaluated in preclinical models *in vivo* for efficacy and safety as required by regulatory authorities.
- Compared to infection with *Pseudomonas aeruginosa* (excluding the agar bead model), mice infected with *Mycobacterium abscessus* can survive for many weeks and form biofilms, which has yielded **better models for studying *M. abscessus* infections *in vivo***.

[6]https://www.ema.europa.eu/en/documents/assessment-report/kalydeco-epar-public-assessment-report_en.pdf

Needs and priorities of people with CF

- **CF is not one disease**, there are over 200 disease causing mutations in the *CFTR* gene. How can we expect a single animal model to represent the plethora of pathologies seen in CF?
- For people with CF, a key challenge is the **burden of care**. Can we focus on reformulating existing therapies to make them easier and less cumbersome to use e.g., towards a once-a-day regime?
- People with CF want **new treatments to reach the clinic as fast as possible**. The ultimate goal is to get new drugs or improved formulations of existing drugs to humans, the pathway to do this needs to be as short and effective as possible, whether or not it includes animal models.

Opportunities

- Current animal models of infection can be useful for investigating PK/PD and safety of new medicines/formulations.
- There are relevant models available to show proof of concept that a drug is effective in CF; many of these models could be useful if simple questions are asked using relevant models.
- It might be useful to conduct a programme of work to analyse and validate a large range of CF preclinical models systematically, testing with CF drugs used in the clinic, to identify which better predict response in the clinic and to see which ones did not predict failure in subsequent clinical trials.
- Bring the CF community together to harmonise protocols used in preclinical models that can be applied based on the needs of the therapeutic and route of administration being evaluated. However, these models should not be used as 'gates' or 'go/no go decisions' and therefore stifle progress for therapeutics that would not be suited for testing in the models.
- Opportunity to educate investors and regulators on the challenges and relevance of using in vivo animal models in CF to influence future funding or regulatory decisions. Meetings of this kind, if organised by a regulator, can have a big impact on the field.

Challenges

- Regulators do not favour microbiology endpoints, especially in later stages of clinical studies. Instead, there is a bigger focus on quality of life and reduction in pulmonary exacerbations. It's therefore critical that we identify **more relevant endpoints** for *in vivo* preclinical studies that better relate to clinical outcome.
- CF is a complex disease that compromises all organs, however preclinical models are generally setup only to study the lungs and therefore do not consider **extra-pulmonary effects**, highlighting an urgent need to model the wider clinical condition.

- There is an urgent unmet need for animal models to test **drug delivery** to the CF lung, and to ensure that appropriate delivery devices exist for use in animal studies, for example the PreciseInhale system for the delivery of dry powder aerosols[7].

- **Preclinical models do not reflect the complex polypharmacy** in CF to enable exploration of optimal dosing, absorption etc., of new drugs alongside other long-term or established treatments.

[7]https://pubmed.ncbi.nlm.nih.gov/29468423/

5 | Clinical Trial Endpoints for CF Infection Clinical Studies

Current state of play

- **Regulators would still like to see FEV_1** as the preferred primary endpoint in CF infection clinical studies. However, in some cases the FDA have accepted CFRSD-CRISS patient reported outcomes (PROs) as primary endpoints in earlier CF infection studies i.e., phase 2b, so this may be evolving.

- For early proof of concept studies, **microbiology endpoints** are frequently used to show proof of concept, however these endpoints are not suitable for later stage trials.

- The current patient reported outcome (PRO) tools e.g., Cystic Fibrosis Questionnaire Revised (CFQ-R), Cystic Fibrosis Respiratory Symptom Diary (CFRSD) and Chronic Respiratory Infection Symptom Score (CRISS) **may not be fit for purpose** for CF infection clinical studies, and separate symptoms from quality of life, without capturing the overall wellbeing of patients.

- In the current era of **highly effective modulators**, there are more people with CF that have mild-moderate disease and improved FEV_1 scores. In future clinical studies, this will make it even more difficult to demonstrate non-inferiority of a new antimicrobial using FEV_1 as a primary endpoint.

Needs and priorities of people with CF

- People with CF feel that **new PRO tools** may be needed to accurately capture what they are experiencing on a day-to-day basis.

- On highly effective modulators, people with CF no longer experience the same symptoms or indicators of an upcoming pulmonary exacerbation. **New biomarkers** that accurately predict long-term outcomes and can be reported alongside PROs would be desirable.

Opportunities

- Development of a **new alternative and more sensitive endpoint** than FEV_1, especially in patients with mild-moderate disease. Lung clearance index (LCI) may be a candidate for this.

- Trials with **composite primary endpoints** of a measurable biomarker (e.g. FEV_1 or microbiology data) and a PRO. This would provide essential data both for regulators and payers. However, the feasibility of these studies in terms of appropriate powering would need to be explored. Alternatively, post-marketing studies for orphan drugs using PROs to demonstrate patient benefit could be explored, however this would require investment from industry.

- Development of more **appropriate PRO tools** that better separate out symptoms and quality of life, and more accurately reflect day-to-day experiences of people with CF. However, validation of new endpoints takes many years and lots of data; correlation with long-term outcomes and response to therapeutic intervention would need to be demonstrated, using measurable data that is considered robust in the natural history of the disease, from patient registries etc. Ongoing research exploring home-reported outcomes of Katfrio[8] will be extremely useful to support future work in this area.

- The identification of PROs alongside **health resource utilization data** could be very interesting e.g. time to symptom resolution and time in and out of hospital.

- Can we **use existing treatments more appropriately**? If have better diagnostic tests and better understand the impact of colonization on quality of life and long-term outcomes, we may be able to use less antimicrobials for a shorter duration, or not at all, and still achieve the same outcomes for people with CF.

- Is there an opportunity to **leverage registry data** to identify long-term outcomes from treatments, by measuring the number of exacerbations experienced?

Challenges

- We **understand little about pulmonary exacerbations** and there is no roadmap for clinical study development.

- For studies looking to **prevent long-term decline** of lung function and quality of life, clinical studies will be timely and costly. How do you balance the needs of regulators vs conducting a time and cost-efficient trial?

- Designing clinical studies to determine efficacy of a **direct antimicrobial** rather than an adjunct therapy will be challenging, as it's unlikely that a placebo arm will be used. Early engagement of regulators on the design of these studies is critical

- It's difficult to understand the **true impact of novel antimicrobials**, as we know many other factors impact on the health and quality of life of people with CF from nutritional and social regimes, physiotherapy, non-antimicrobial therapies and even rest. It's been shown that taking the same antibiotic in the hospital rather than at home results in improved FEV_1 responses. How can we factor all these considerations into future studies?

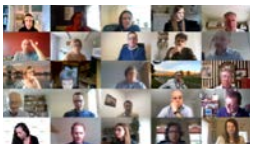
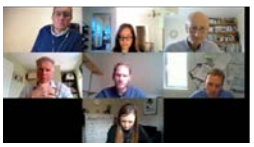
- In some cases, when people with CF are prescribed antimicrobial treatments, they can often feel worse before they start to feel better. **Relying solely on PROs may therefore be misleading** in the short-term. There's a need for better validation studies, potentially linking PROs to biomarkers to better predict treatment response.

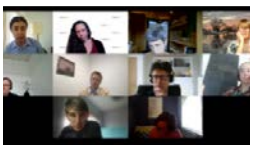
[8]First-of-Its-Kind Study Uses Smartphone to Track Cystic Fibrosis in Real Life | CF Foundation

Appendix 1 | TPP Virtual Symposium Delegates

Name	Affiliation
Prof Alan Smyth	Professor of Child Health, School of Medicine (& NIHR Nottingham Biomedical Research Centre), University of Nottingham
Dr Alessandra Bragonzi	Head of Infection and Cystic Fibrosis Unit, Director CF animal Core Facility, Ospedale San Raffaele, Milano, Italy
Dr Alessandra Gaeta	Programme Director, Medicines Discovery Catapult
Alice Porter	Deputy Director of Commercialisation, UKRI
Prof Andres Floto	Wellcome Trust Investigator and Professor of Respiratory Biology in the Molecular Immunity Unit of the University of Cambridge (based at the MRC Laboratory of Molecular Biology), Research Director of the Cambridge Centre for Lung Infection at Royal Papworth Hospital, and Director of the UK Cystic Fibrosis (CF) Innovation Hub.
Andrew Ball	Therapy Area Lead for Cystic Fibrosis, Chiesi Ltd
Angelo Micciche	Person Living with CF
Anne Mosekjær Graver	Associate Director Clinical Development, AlgiPharma AS
Dr Beverley Isherwood	Programme Manager, Medicines Discovery Catapult
Dr Brett Baker	President and Chief Innovation Officer, Microbion Corporation
Dr Cara Cassino, M.D	Executive Vice President of Research & Development, Chief Medical Officer, ContraFect Corporation
Dr Carsten Schwarz, MD, assoc. Prof. (PD)	Director Division of Cystic Fibrosis, Department of Pediatric Medicine, CF Centre Potsdam
Dr Charles McOsker	Chief Scientific Officer, Clarametyx Biosciences
Dr Christian Zwingelstein	Clinical Scientist, Anti-infectives, Polyphor Ltd
Prof Clive Page	Professor of Pharmacology, King's College London
D.R. (Dutch) VanDevanter PhD	Adjunct Professor of Pediatrics, Case Western Reserve University School of Medicine
Dr Deborah O'Neil	CEO, NovaBiotics
Dr Derek Lindsay	COO, Infex Therapeutics Limited
Dr Dom Pollard	Analyst, Opportunity Assessment Group, LifeArc
Dr Drew Matheson	Executive Director. Franchise Area Lead Respiratory Medicine and Infectious Disease, Worldwide Clinical Trials
Dr Felix Ratjen	Program Head, Translational Medicine, SickKids Toronto
Dr Frederik Deroose	CKO, AGILeBiotics
Jacob Bradbury	CF Researcher and Person Living with CF
Jade Ashton	Person Living with CF
Dr Jamie Duckers	CF consultant, All Wales Adult CF centre, Cardiff and Vale University Health Board
Prof Janis Shute	Professor of Respiratory Pharmacology, University of Portsmouth
Prof Jane Davies	Professor in Paediatric Respirology & Experimental Medicine at the National Heart and Lung Institute and an Honorary Consultant in Paediatric Respiratory Medicine at the Royal Brompton & Harefield NHS Foundation Trust

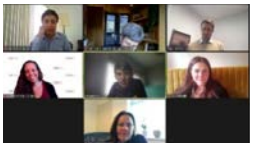
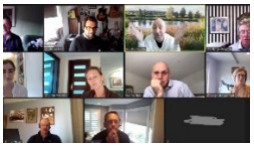


Jeanette Mucha	CEO & Cofounder, SciBac Inc.
Dr Jessica Boname	Head of Programme, Antimicrobial Resistance, Medical Research Council, UK Research & Innovation
Jessica Lee	Senior Programme Manager, Medicines Discovery Catapult
Dr Jo Fothergill	Senior Lecturer, University of Liverpool
Dr Johnny Cordiner	CFO & Commercial Director, Lamellar Biomedical Ltd
Dr Jörg Haupenthal	Project Manager, Helmholtz Centre for Infection Research
Katherine Cowan	Independent Facilitator
Dr Laura Fregonese MD, PhD, Clin Epi (MSC), EMDM	Clinical Specialist Respiratory Medicine, Immunology and Vaccines Paediatric Medicines and COVID-19 Task Force, European Medicines Agency (EMA)
Lorna Allen	Involvement Manager, Cystic Fibrosis Trust and Parent of a Child with CF
Dr Lucy Allen	Director of Research, Cystic Fibrosis Trust
Luke Twentyman	Person Living with CF
Dr Maria Uria-Nickelsen	Alliance Director, CARB-X
Alliance Director, CARB-X	CEO, National Biofilms Innovation Centre
Dr Mark Sutton	Scientific Leader, Public Health England
Dr Martin Everett	CSO, ANTABIO
Dr Michael Graz	CEO Biophys Ltd
Dr Miles Denton	Consultant Microbiologist, Leeds Teaching Hospitals NHS Trust
Dr Mina Pastagia MD	VP of Clinical Development, Armata Pharmaceuticals
Dr Nadia Cohen PhD	Alliance Manager, CARB-X
Dr Nel Moore	Director, FWEast Consulting
Dr Paula Sommer	Head of Research, Cystic Fibrosis Trust
Dr Peter Warn	Consultant, Magic Bullet Consulting Ltd
Dr Phil Packer	Innovation Lead-AMR and Vaccines, Innovate UK
Dr Richard Amison	Lecturer in Pharmacology, King's College London
Dr Rida Mourtada	Chief Scientific Officer, Lytica Therapeutics
Dr Ryan Cirz	Chief Executive Officer, Revagenix, Inc.
Dr Sarah Brockbank	Lead Scientist, External Drug Discovery, Medicines Discovery Catapult
Dr Shruta Rege, Ph.D.	Vice President and Head of Global Regulatory Affairs, Entasis Therapeutics
Dr (Anthony) Simon Lynch	Senior Scientific Director and Janssen Fellow, Infectious Diseases and Vaccines, Janssen R&D LLC.
Dr Steven Tait	Senior Business Manager, LifeArc
Prof J. Stuart Elborn MD	Pro-Vice-Chancellor, Faculty of Medicine, Health, and Life Sciences and Professor of Medicine, School of Medicine, Dentistry, and Biomedical
Dr Su Chiang	Alliance Manager, CARB-X
Dr Suba Srinivasan MD MPH	Senior Medical consultant, Bugworks
Dr Tiffany M. Burnett	Senior Director, Biopharma Programs, Cystic Fibrosis Foundation
Thomas Larsson	Product Lead, Vaccines and therapies for infectious diseases, Human Medicines Division, European Medicines Agency (EMA)



Appendix 2 | TPP Virtual Symposium Agenda

Time	Session	Speaker
12.50 – 13.00	Arrival onto Zoom call	
Introductions to the TPPs		
13.00 – 13.15	Welcome and Introduction	Katherine Cowan
13.15 – 13.25	The unmet needs and burden of care faced by people with CF: why these TPPs are important	Luke Twentyman
13.25 – 13.35	TPP development process and feedback from the Delphi analysis	Jessica Lee
13.35 – 13.45	Q&A	All delegates
Feedback on the TPPs		
13.45 – 13.50	Introduction to the breakout groups	Katherine Cowan
13.50 – 14.35	Breakout discussions	All delegates
14.35 – 14.45	Break	
14.45 – 15:30	Breakout discussions	All delegates
15:30 – 15.55	Final feedback session	Katherine Cowan
15:55 – 16.00	Closing remarks	Dr Lucy Allen
Meeting close		

Breakout Discussion Information

Duration of Antimicrobial Treatment, Chaired by:
Prof Andres Floto - University of Cambridge, Royal Papworth Hospital & UK Cystic Fibrosis (CF) Innovation Hub
Dr Jamie Duckers - Cardiff and Vale University Health Board

The TPPs outline treatment durations that people with CF would ideally like from new antimicrobial treatments, including whether treatments could be delivered at home or in a primary care setting. The Delphi survey revealed a lack of agreement on the proposed ideal treatment durations for drugs that target *Mycobacterium abscessus* eradication or pulmonary exacerbations.

This breakout session aims to discuss:

- Are the wishes of people with CF in terms of treatment duration achievable?
- What factors need to be considered during drug development to ensure new drugs have treatment durations that meet the needs of people with CF?
- What further research or work is required to provide better guidance in this area?

Preclinical Models for CF Antimicrobial Development, Chaired by:
Dr Jo Fothergill, University of Liverpool
Prof Clive Page and Dr Richard Amison, Kings College London

Results from the Delphi survey indicate a strong agreement that the range of *in vitro*, *ex vivo* and *in vivo* assays suggested in the TPPs is useful, and in addition it highlighted a strong agreement that preclinical studies should be performed in both artificial sputum media and sputum samples. However, there was less consensus on whether generic rodent infection models (e.g., mouse thigh model or rodent pulmonary infection model) are appropriate for use in CF antimicrobial preclinical studies, in place of CF specific infection models.

This breakout session aims to discuss:

- Current CF animal models: what's available and are any suitable for use in CF antimicrobial preclinical studies (and for which organisms e.g., *Pseudomonas aeruginosa*, *Mycobacterium abscessus*)?
- What is the relevance of non-CF infection models e.g., mouse thigh model or rodent pulmonary infection model, for CF antimicrobial studies?
- What further research or work is required to provide better guidance in this area?

Clinical Trial Endpoints for CF Infection Clinical Studies, Chaired by:
Prof Jane Davies, National Heart and Lung Institute & Royal Brompton & Harefield NHS Foundation Trust
Dr Deb O'Neil, Novabiotics

The TPPs propose that patient reported outcomes (e.g., CFRSD-CRISS, CFQR) should be recommended as primary endpoints for CF infection clinical studies. The results from the TPP survey suggest a lack of agreement on this. However, the Delphi survey did indicate a strong agreement that FEV_1 and microbiology data should not be recommended as primary clinical trial endpoints.

This breakout session aims to discuss:

- Current guidance/thinking from regulatory bodies and case studies of where patient reported outcomes have been used as primary clinical trial endpoints in CF infection studies.
- Opportunities and challenges associated with using patient reported outcomes as primary endpoints in CF infection clinical studies.
- What further research or work is required to provide better guidance in this area?

Acknowledgements

The core team responsible for the development of the Patient-Focused TPPs for CF-Related Infections is:

- **Dr Alessandra Gaeta**, Medicines Discovery Catapult
- **Dr Jamie Duckers**, Cardiff and Vale Health Board
- **Jessica Lee**, Medicines Discovery Catapult
- **Lorna Allen**, Cystic Fibrosis Trust
- **Dr Mark Sutton**, Public Health England
- **Dr Paula Sommer**, Cystic Fibrosis Trust
- **Dr Richard Amison**, Kings College London

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