Accelerating Antibiotic Development

Innovative clinical trial platform

Business Plan

Funded by Wellcome Drug Resistant Infections Program
Produced by tranScript Partners and Syneos Health

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Abbreviations

Abbreviation	Definition
ABSSSI	Acute Bacterial Skin and Skin Structure Infection
AML	Acute Myeloid Leukaemia
AMR	Antimicrobial Resistance
ARLG	Antibacterial Resistance Leadership Group
BARDA	Biomedical Advanced Research and Development Authority
BD	Business Development
CABP	Community-Acquired Bacterial Pneumonia
CARB-X	Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator
CCT	Common Control Trial
CEO	Chief Executive Officer
CMO	Chief Medical Officer
CPD	Continuous Professional Development
CRC	Clinical Research Collaboration
CRO	Contract Research Organisation
CSO	Chief Scientific Officer
CTA	Clinical Trial Application
cUTI	Complicated Urinary Tract Infection
DNDi	Drugs for Neglected Diseases Initiative
EA	Executive Assistant
EC	Ethics Committee
EDC	Electronic Data Capture
EFPIA	European Federation of Pharmaceutical Industries And Associations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FPFV	First Patient First Visit
FTE	Full-Time Equivalent
GARDP	Global Antibiotic Research and Development Partnership

Abbreviation	Definition
GCP	Good Clinical Practice
GCTCA	Global Clinical Trial Centre Alliance
HAP	Hospital-Acquired Pneumonia
HR	Human Resource
HTA	Health Technology Assessment
IMI	Innovative Medicines Initiative
IMPACT	International Master Protocol Alliance Clinical Trial
IMPACT DIGITAL	IMPACT division responsible for data handling and digital management
IMPACT GCTCA	IMPACT division responsible for site training and management
IMPACT ProDIO	IMPACT division responsible for development, implementation and oversight of the individual protocols
IRB	Institutional Review Board
LPLV	Last Patient Last Visit
MDR	Multi-Drug-Resistant
NIAID	National Institute of Allergy and Infectious Disease
OECD	Organisation for Economic Cooperation and Development
PENTA-ID	Paediatric European Network for the Treatment of AIDS and Infectious Diseases
PK	Pharmacokinetic
PM	Project Management
PR	Public Relation
PVG	Pharmacovigilance
Q	Quarter
RFP	Request for Proposal
SOC	Standard-of-Care
UK	United Kingdom
US	United States
VAP	Ventilator-Associated Pneumonia
WHO	World Health Organisation
XDR	Extensively Drug Resistant

Executive Summary

New antibiotics are essential to combat resistance

Bacterial infections are a fundamental public health issue and the incidence of serious infections is increasing, in part due to the greater use of life enhancing/prolonging treatments.

The Organisation for Economic Cooperation and Development (OECD) recently published a report (OECD Health Policy Studies, 2018), which stated that in the period 2015 to 2050, 2.4 million people could die in Europe, North America and Australia due to resistant infections. Whilst 1.6 million of their lives could be saved by good stewardship, mass media campaigns and rapid diagnostic tests, many may continue to die unless we tackle the challenges related to the development of new antibiotics. Unfortunately, many of the deaths due to resistant bacteria occur in hospitals where mass media campaigns, though helpful, have less impact. The number of deaths in the United Kingdom (UK) alone rose from 2016 to 2017 by 38.8% and almost all occurred in hospitals. The OECD report acknowledges that many of the infections are caused by bacteria such as *Klebsiella*, *Staphylococcus* or *Pseudomonas*, which are commonly drug-resistant hospital pathogens.

The International Master Protocol Alliance Clinical Trial (IMPACT) is an initiative based on an approach devised by a small group of scientific experts (Larsen 2016, McDonnell, Rex et al. 2016) to facilitate the development of badly needed hospital antibiotics.

IMPACT will not only act as Push and Pull incentives to the pharmaceutical industry and diagnostics companies, but also will have a powerful impact on improving information vital for stewardship in hospitals, education of intensive care staff and will bring together the stakeholders involved in fighting antimicrobial resistance in a unique collaborative manner. This collaborative initiative will drive efficiencies, reducing the amount of funds that the society needs to put into research and development of antibiotics to obtain the necessary knowledge required for effective stewardship and education.

Why collaboration in clinical trials is essential

Antibiotic clinical trials are required to characterise benefit risk and provide effective labelling needed for effective stewardship. The greatest medical need for antibiotics are resistant hospital infections, especially those caused by Gram-negative bacteria. As the clinical outcomes of infections vary depending on the organ/body system, each type of infection has to be studied separately. The more serious the infection, the more difficult the studies are to conduct and to interpret. Thus, the first indication typically studied in Phase 3 clinical trials of Gram-negative antibiotics is typically the complicated urinary tract infection (cUTI), usually less serious than other infections but easier to interpret in terms of the performance of the studied antibiotic. The cUTI indication however does not provide sufficient information as to how well the antibiotic will perform in the more serious conditions such as hospital acquired pneumonia (HAP), ventilator associated pneumonia (VAP) or bloodstream infections, which are often related to sepsis and associated with high mortality. The initial treatment indication such as cUTI will achieve a licence for the drug to be put on the market, but more investment has to be made to make the new antibiotics available for patients with more serious infections and inform adequate stewardship.

However, even if the initial indication is achieved and subsequent indications are studied, a research programme must be conducted to allow safe use of these antibiotics in children. The paediatric programme is a legal requirement for anybody who registers a new drug of any sort.

IMPACT is designed to make those clinical trial programmes more efficient, generating essential information for both less and more serious infections as well as for the paediatric patient population.

In summary, IMPACT offers unique underpinning to the antimicrobial resistance efforts:

- It will reduce the total cost of generating benefit-risk and vital stewardship information for new antibiotics.

- It will bring antibiotics to the market faster for indications and populations where they are most required.

- It will, by driving collaboration, work towards sustaining an ecosystem that allows pharma, private philanthropy, regulators, public health, academia and, above all, prescribers and clinicians to work together to generate research and educate the healthcare providers to effectively fight antimicrobial resistance.

Should this model of collaboration work in combating antimicrobial resistance by providing better information for prescribing healthcare workers, then such clinical trial methodology could be effectively rolled out into other therapeutic areas.

Why are clinical trials so expensive and how can IMPACT reduce the cost?

Currently, each Sponsor conducting clinical trials custom-builds a single-use network of between 50 and 200 sites per study conducted, with staff at each site in the network needing to be trained in the study protocol. Sponsors incur huge costs in opening and re-activating multiple study sites for every new agent that is developed. Because clinical studies arise at irregular intervals, contract research organisations (CROs) cannot maintain one network for a range of companies, and sites sporadically used are of variable quality. A more efficient system could be much cheaper.

Several government and collaboratively funded trial networks have been, or are being, set up to facilitate implementation of antimicrobial clinical trials but currently rarely interact. A global clinical trials network would be extremely valuable in providing education to clinical trial sites all over the world and offering a high standard of research, in which novel powerful clinical trial designs could be applied. This would reduce costs and potentially generate a broader base of robust information for both regulation and antibiotic stewardship.

Innovative trial designs, where more than one test agent is compared to a single control, have driven collaboration between Sponsors with the common aim of allowing development of drugs in populations where there are limited numbers of patients. A similar study design for antibiotic trials could be used to speed up the trial process, to get antibiotics to the market sooner and at reduced cost. In this design several new antibiotics would be studied in one trial sharing a control group, which would be a standard comparator treatment.

IMPACT aims to increase the speed to market, offer cost reduction, generate more robust information and innovate trial methodology by its two main components:

- A Global Clinical Trial Centre Alliance (GCTCA) of qualified trial sites implementing the Common Control Trial (CCT) methodology.

- A new design of clinical trials, based on a CCT.

Global Clinical Trial Centre Alliance network

The GCTCA will develop a network of high quality, clinical trial sites by setting standards and collaborating with other existing trial unit alliances. The network aims not only to offer a platform for antimicrobial clinical research but also a vehicle to encourage education of all involved healthcare providers who may treat infections in patients eligible to enter the network trials. This has several exciting advantages, including the spin-off of trained clinical researchers to undertake work with new diagnostics or new methodologies that may be vital for understanding antibiotic stewardship in hospitals.

Additionally, the clinical trial network will reduce costs of clinical research as:

- Site selection and set-up activities before starting a trial will be avoided due to the existence of a group of established trial units **leading to much shorter run in time and all sites starting at the same time.**

- Pre-set relationships/collaborations with other departments in the hospital will lead to a bigger pool of patients, **resulting in faster and greater recruitment of patients per trial site**.

- Pre-emptive study management by permanently employed and highly trained site trial co-ordinators will **lead to the reduced need for oversight**.

- It will offer an opportunity for implementation of **innovations to trial conduct and more efficient collection and analysis of patient generated data.**

In addition, the network is essential for implementation of the CCT methodology.

The CCT design

In traditional, randomised, controlled trials (RCTs), patients are randomised to a control treatment or to the test treatment. CCTs compare more than one treatment to a control or more than one dose of the same treatment to a control. Such designs are routinely used in drug development, especially for dose ranging studies and combination treatments. IMPACT is proposing for two or more Sponsors to compare two test treatments to control in the same study. Test treatments may start at the same time or at different times and the control group may run continually.

The CCT design offers several advantages:

- Fewer control patients are required when antibiotics share the same control group, with the time **to complete the trials and the cost being reduced.**

- Sites are continuously enrolling control patients from the outset of the study reducing the **time to trial start being reduced.**

- Different test agents are assessed in the same trial centres, with more comparable and robust data being generated **for benefit-risk assessment and for antimicrobial stewardship.**

Proposed highest medical need trials to be support by IMPACT

After consultation with many stakeholders including pharma and biotech companies and regulatory bodies, three clinical programmes have been proposed for the IMPACT initiative. These include paediatric trials in mixed indications and adult trials in HAP/VAP and cUTI.

New antibiotics pipeline for IMPACT

The potential market for IMPACT is large. As of May 2018, there were 153 agents in pre-clinical development, 25 in Phase 1, 24 in Phase 2, 12 in Phase 3 and 5 undergoing regulatory review either in the European Union (EU) or the United States (US). Majority of the Gram-negative antibiotics currently in pre-clinical or Phase 1/2 clinical development would be eligible for the cUTI indication.

Few compounds have recently been studied for the treatment of HAP/VAP (exceptions being Zerbaxa and Avycaz), these serious infections need to be studied separately from cUTI as doses required may be different and otherwise treatments may be used off label potentially putting patients at risk and driving resistance through selection. Nine antibiotics could be studied in HAP/VAP in 2020 and a further 10 between 2021 and 2023.

There are 18 recently licensed antibacterial agents that will need to initiate paediatric studies between 2019 and 2021.

Does IMPACT justify the investment?

The benefit to society of bringing new antibiotics to the market and better quality of information for stewardship and prescribing is incalculable. OECD predict that, in spite of their proposed measures using good stewardship, mass media campaigns and diagnostics, almost 1 million people will die during the period 2015 to 2050 of infections caused by resistant bacteria. Many of these deaths will occur in hospitals and research that may reduce this rise in mortality is vital.

The research savings to be achieved by collaboration of Sponsors, government and private philanthropists via IMPACT is estimated at greater than 30% of the original costs. Even with the cost of the infrastructure required to run IMPACT, the savings to the clinical trial ecosystem are substantial. It is estimated that clinical trials for drug development cost $40 billion annually. If IMPACT methodology and networks became common place in drug development, the savings to the healthcare system could run to billions. If, as collateral, the data generated were of better quality and lead to improved regulatory and stewardship processes, this would be an additional important benefit to healthcare. Clinical research methodology is rapidly evolving, and IMPACT could be a valuable part of this evolution.

Conclusion

The purpose of this Business Plan is to evaluate the cost efficiencies of IMPACT and the likely cost to private and government funds to initiate it.

1 IMPACT, A New Solution to Antibiotic Drug Development

1.1 Market Need

There is a clear and undisputed need for new antibiotics. Currently, approximately 700,000 people die from infections caused by antibiotic-resistant pathogens every year and, it is estimated that 10 million lives each year, and a cumulative 100 trillion USD of economic output, will be at risk by 2050. Furthermore, loss of antibiotic effectiveness with time will jeopardise routine and/or emergency medical procedures such as caesarean sections, joint replacements, or gut surgery, as well as make life-prolonging treatments (such as cancer chemotherapy) too dangerous to undergo (O'Neill 2016).

New antibiotics however, are not easy to discover; their clinical development is challenging due to regulatory requirements as well as difficulties in showing adequate efficacy and safety profiles, and the likelihood of successfully moving an antibiotic through the clinical development stages to market is relatively low (Projan 2003, Simpkin, Renwick et al. 2017). For example, of the 39 antibiotics in Phases 1 to 3 (The Pew Charitable Trusts 2018) as of March 2017, only 13 (33%) are anticipated to become marketable products because of the expected attrition rate (Simpkin, Renwick et al. 2017).

Even if new agents do reach the market, due to their improved ability to fight drug resistant bacteria, they will frequently be reserved for last-line use (Taylor 2018). Furthermore, because antibiotics tend to be only modestly priced, and because they are generally administered only for short durations compared with other therapeutic agents (e.g. oncology treatments), the return on investment is considered by companies to be relatively low (Projan 2003). This combination of scientific challenges and poor commercial attractiveness has created a strong disincentive for pharmaceutical companies, compared with other therapeutic areas, and has become a substantial driver for reduced research efforts (Rex, Goldberger et al. 2014). Indeed, several large pharmaceutical companies have now withdrawn completely from antibiotic development in favour of more profitable therapeutic areas, Novartis, AstraZeneca, Bristol-Myers Squibb and Eli Lilly being recent examples (Taylor 2018). Whilst all kinds of initiatives are in place to fill this void, such as government and private Push and Pull funding, regulatory approaches to earlier limited registration and government partnerships with pharma, all require extensive funding for clinical trials.

All new antibiotics must, of course, demonstrate an appropriate benefit-risk profile and generate data supporting antibiotic stewardship. However, the cost and long duration of antibiotic clinical trials can be a significant barrier to bringing new treatments to patients. The most expensive part of the clinical development process is the need for multicentre clinical trials. With acute infections progressing rapidly, companies conducting anti-infective studies often incur huge costs in opening and re-activating multiple study sites for every new agent that is developed. Currently, to obtain regulatory approval of an anti-infective agent, it is necessary for each Sponsor conducting clinical trials to custom-build a single-use network of sites for each study conducted, often requiring between 50 and 300 sites that can enrol patients 24 hours a day. Each of these networks has predictable operational start-up issues, for example, the staff at every site need to be trained in the study protocol. Adding to this problem, because clinical studies arise at irregular intervals, CROs cannot maintain one network for a range of companies while the sites themselves may have difficulty maintaining experienced study personnel.

In 2016, the Food and Drug Administration (FDA) estimated that approximately 25 antibacterial drugs would have completed, or would enter the late stages of, clinical development in the next few years. If multiple companies set up and run their own clinical trials in the same indication at the same time, finding patients would become increasingly difficult and will inevitably slow down development (McDonnell, Rex et al. 2016). Making the clinical trial system more efficient would both reduce the cost of antibiotic development and make it easier to deliver new agents to fight antibiotic-resistant bacteria. This is the objective of the Innovative Medicines Initiative (IMI) COMBACTE, an IMI initiative now in its fifth year [2018], which has set up an alliance of over 850 trained hospitals and 650 trained laboratories across Europe which are ready to support Phase 2 and 3 clinical trials of new antibacterial drugs.

In other therapeutic areas however, innovative trial designs have been utilised, rather than the conventional Phase 2 and 3 approach, whereby more than one test agent is compared to a single control. For example, the Beat acute myeloid leukaemia (AML) Master trial (https://www.lls.org/beat-aml), is an initiative in

which several companies collaborate with academic institutions with the common aim of developing targeted treatments for patients with AML. A similar study design set-up specifically for antibiotics would provide clinical trial site longevity, and allow continuous enrolment of patients, thus accelerating development pipeline.

Such an innovative trial design in the area of antibacterial development would be most efficiently managed through an alliance of multiple stakeholders, with the common goal of facilitating and expediting clinical research of new antibacterial drug candidates in key indications (e.g. cUTI or HAP/VAP).

1.2 IMPACT Alliance

The International Master Protocol Alliance Clinical Trial (IMPACT) is an initiative based on an approach devised by a small group of scientific experts (Larsen 2016, McDonnell, Rex et al. 2016) to resolve the challenge of the large clinical trials which must be undertaken to assess benefit-risk of new antibiotics.

IMPACT aims to capitalise on the existing collaboration among representatives of the antibiotics stakeholder community (e.g. Pharma/Developers, Sites/Investigators, Patients, Regulatory Authorities, Push Funds, etc), driving innovation in clinical trial design and bringing antibiotics to the market faster (or allowing extension of the approved indications beyond the initial label), while maintaining the stringent benefit-risk assessment required to protect public health.

The IMPACT concept comprises two components:

- A new design of clinical trials, based on a common control trial (CCT) design, which reduces the number of control patients required for assessment by sharing them between test treatments.
- A GCTCA with qualified trial sites to allow the CCT methodology to be implemented and to support and improve trial centre standards and adoption of innovation.

The combination of the two elements is a powerful tool, which offers many opportunities not just for antibiotic development but potentially in many other therapeutic areas.

The key principles behind the IMPACT initiative are a) collaboration between multiple stakeholders in antibiotic development, b) sharing of the control group using the new CCT methodology and c) efficiencies associated with sharing high quality clinical trial centres (Figure 1).

IMPACT is planned as a public-private partnership collaboration aimed at improving the efficiency of clinical trials and generating benefit-risk evidence needed to bring antibiotics to the market faster. It is a natural progression from individual Sponsors and CROs working in silos.

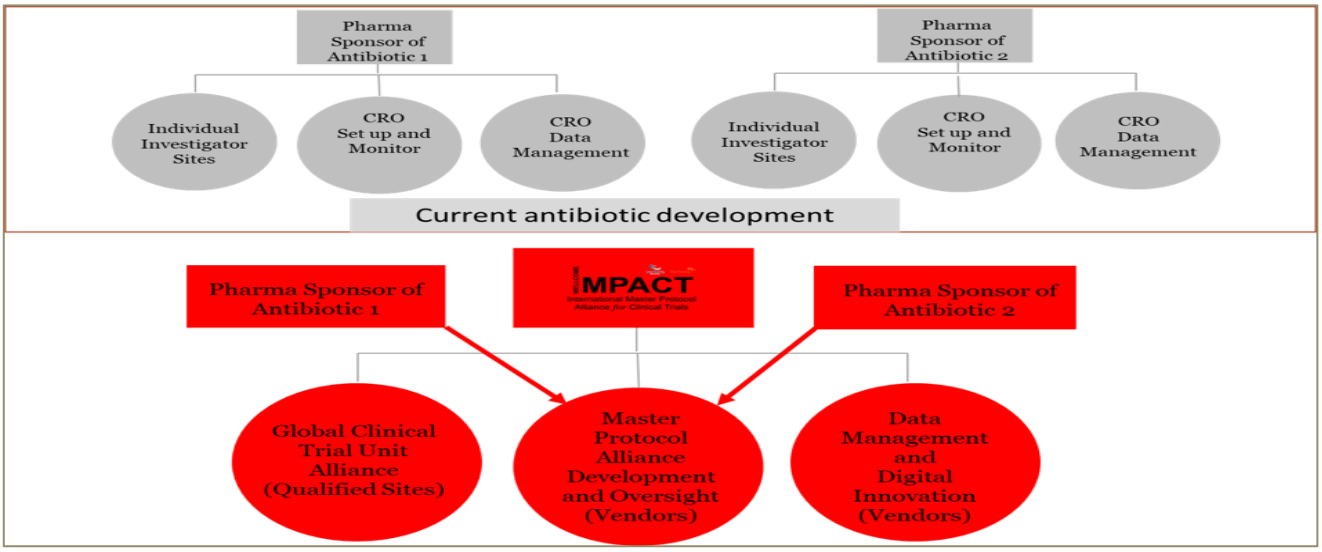

Figure 1: Current antibiotic development paradigm and IMPACT

CRO: contract research organisation; IMPACT: International Master Protocol Alliance Clinical Trial

1.2.1 Common Control Trial Design

In traditional, RCTs, patients are randomised either to the control group or to the active treatment group. The most powerful randomised control design is when patients are randomised in equal numbers to each group, control and test treatment. When comparing more than one treatment to control or more than one dose of the same treatment to control in the same study, patients are usually randomised equally to all test treatments and control. Such designs are routinely used in drug development, especially for dose ranging studies and combination treatments. IMPACT is proposing a new approach to the CCT design, whereby two or more different Sponsors participate in the same trial, each comparing their drug to the control group, but neither being aware of the results of the other test agent.

The CCT design has efficiencies associated with sharing the control group, which have significant implications. For example, based on the methodology of McDonnell et al, and using the number of patients required for a HAP/VAP trial (EMA 2013, FDA 2014, McDonnell, Rex et al. 2016), Phase 3 trials currently needed for registration of 3 drugs would require 1800 subjects in total (600 subjects per trial, with 300 subjects on test drug and 300 on control, totalling 900 subjects on test drugs and 900 on control). Simply by sharing controls and conducting a study with 3 treatment arms and a single control arm (with 1:1:1:1 randomisation ratio) only 25% of subjects are randomised to the control arm, and subsequently only 1200 subjects (900 on test drugs and 300 on control) are needed. Therefore, each drug being developed benefits from a 33% reduction in patient numbers (McDonnell, Rex et al. 2016).

Figure 2 provides a simple visual representation of the standard CCT methodology.

Figure 2: Schematic of standard CCT design

However, in reality, there will be few situations where three Sponsors might want to conduct a single trial at exactly the same time and, therefore, IMPACT has had to evolve the design beyond the simple randomised CCT as described above. The trial designs proposed by IMPACT takes the common control principle to the next stage and introduces staggered start and enrolment periods for the different test drugs, thus accommodating varying timelines of the different development programmes. In this adaptive CCT design the control group will be continuously recruited into the study and will provide a pool of control patients that could be used in assessment of multiple test treatments. The adaptive CCT design reduces the overall patient numbers needed, while allowing introduction of test drugs into the IMPACT trial in a flexible way.

Figure 3 presents the adaptive IMPACT CCT methodology.

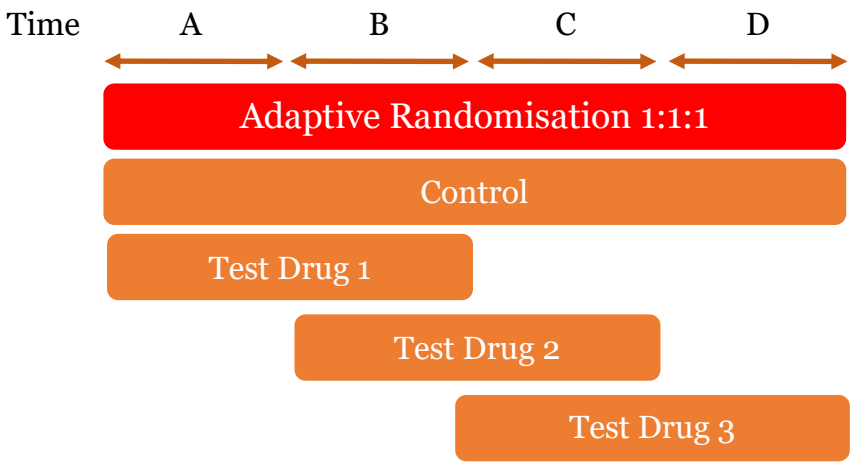

Figure 3: Schematic of adaptive CCT design

During time period A, patients will be randomised using a 1:1 randomisation ratio to Test Drug 1 or the control arm. At the start of time period B when Test Drug 2 is introduced into the study, the randomisation pattern will change, and patients will be randomised using a 1:1:1 randomisation ratio to Test Drug 1, Test Drug 2 or the control arm. At the start of time period C, when Test Drug 1 has recruited sufficient patients to leave the study and Test Drug 3 is introduced into the study, the randomisation will change again, and patients will be randomised using a 1:1:1 randomisation ratio to Test Drug 2, Test Drug 3 or the control arm. Similarly, at the end of time period C, when Test Drug 2 comes out of the study, randomisation will revert to the 1:1 ratio for Test Drug 3 or the control arm.

In its simplest form (Figure 3) the assessment of each Test Drug would be conducted using patients recruited within the time periods when patients were being randomised to that Test Drug. For example, when comparing Test Drug 2 with the control arm, those patients randomised to Test Drug 2 or control in time periods B and C would be included. This approach is described as using Concurrent Controls.

The design not only reduces patient numbers but it also shortens start-up time due to sites actively enrolling from Day 1. The assessment of different test agents in a single study, all under the same trial design and trial conditions will generate consistently robust homogenous data potentially further reducing the number of patients. The continuously running control group also offers data to answer regulatory and scientific questions, epidemiology in clinical trials, evaluating development of better outcome criteria and implementation of innovative tools of patient generated data.

Conducting the IMPACT study using an adaptive CCT design will also allow evaluation of an even more innovative clinical trial methodology, which could potentially further reduce the size of clinical studies. Such an innovative approach would be based on the use of Non-concurrent Controls, where the control group continuously recruited into the study (but not randomised at the same time as a given test agent) would provide a pool of control patients that could be used to 'top-up' the control arm. Such a design would offer additional savings and a possibility to further expedite the conduct of clinical trials.

The IMPACT adaptive CCT design advantages:

- *The cost and time required to complete trials are reduced - fewer control patients and start-up time reduction.*
- *Comparable, robust data obtained as different test agents are assessed in a single study.*
- *Patient data available for additional regulatory or scientific research.*

1.2.2 Global Clinical Trial Centre Alliance

The IMPACT methodology requires high quality, skilled trial units, which will operate in a standardised manner over a long period of time, thus offering the opportunity to utilise innovative ways of trial management.

Established trial unit networks avoid the need for site selection and set-up activities before starting a trial. IMPACT plans to set up such a group, the GCTCA, using both new centres and existing networks.

A summary of differences between network clinical trial units and individual investigator sites is shown in Table 1.

Table 1: Clinical trial unit vs individual investigator sites

Single Investigator Site	Clinical Trial Units	How IMPACT Creates and Leverages the Clinical Trial Unit Concept
CROs have to establish investigator's understanding of the clinical trial design. Many physicians have no training in clinical research	IMPACT plans to train staff and accredit them alongside existing networks so they become experienced in trial design	IMPACT supports the development of highly trained investigators and generates consistently better quality data
Usually has access to own patients only and has no control over standards of corroborating physicians in the hospital	Has access to a broader collection of hospital departments with existing contracts, standards and communications established	Increases speed and quality of recruitment in each site
Difficult to implement clinical trial methodological and technological innovations due to short term involvement of the site in single trials	Long term involvement - Innovations in trial conduct easier (e.g. patient pre-consent and wearable technology that will allow patients to be closely monitored when discharged home) and the more efficient collection and analysis of patient generated data	Sites constantly keep up with regulatory and technical innovations benefitting sponsors and patients in trials
Short term involvement means sites often have to recruit a trial co-ordinator for the period of the trial - often not trained in clinical research and is filling an interim role compromising specific training programmes	Long term involvement means professional trial co-ordinators and fully trained physicians available to conduct all aspects of clinical trials, including more technical aspects such as PK or specialist microbiology	By providing continuous work justifies training and CPD for trial centre staff maintaining trials skills and quality recruitment and care of patients

CPD: continuous professional development; CRO: contract research organisation; IMPACT: International Master Protocol Alliance Clinical Trial; PK: pharmacokinetic

Global trial units will be chosen or set up, based on expertise and training of the staff in the understanding and conduct of clinical trials involving antimicrobial investigational products. Studies will need to be conducted in compliance with the local regulations, the EU Directive for Clinical Trials and FDA regulations and may require further training of current staff or recruitment of specialist staff. Registration schemes such as UK Clinical Research Collaboration (UKCRC) require high standards and are required to provide evidence to an international panel of experts regarding their capability to centrally coordinate multicentre clinical trials and to ensure conduct and delivery of clinical trials to the highest quality standards. It is the intention for IMPACT to develop and apply a similar approach for the GCTCA sites.

The GCTCA will involve qualified trial sites that will allow the CCT methodology to be implemented, support and improve trial centre standards, and facilitate the adoption of innovations implemented in clinical research. The GCTCA will build on the work of many other trial unit alliances such as IMI Combacte, Antibacterial Resistance Leadership Group (ARLG), UKCRC, Beat AML and many other initiatives in oncology and rare diseases.

IMPACT GCTA trial network advantages:

- *Avoidance of need for site selection and set-up activities before starting a trial*
- *Pre-set relationships/collaborations within the hospital will lead to more rapid recruitment*
- *Improved quality will lead to more homogenous patient data set*
- *Improved quality and innovation in risk-based monitoring will reduce sponsor Good Clinical Practice (GCP) resource*

- *Site co-ordinators will develop a deep understanding of the challenges faced in antibiotic trials*
- *Innovations in trial conduct lead to more efficient collection and analysis of patient data*

2 Stakeholders

2.1 Stakeholder Profiles

Potential providers of test agents: Sponsors who own the antibiotics in development and funding partners (public and private) who provide financial support for the programmes and are the target clients of IMPACT. The public organisations that provide funds to antibiotic development include the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), Gates Foundation, Biomedical Advanced Research and Development Authority (BARDA), as well as Innovate UK and an array of public and private supporters globally.

Regulators, public health and prescribers: Critically important to the clients are regulators who approve the drugs, although regulators could also be considered one of IMPACT's clients through their potential interest in the control group data. Pharmaceutical companies will also need to ensure the data generated are adequate for health technology assessment (HTA) organisations and prescribers, who will need appropriate information to evaluate the antibiotic for formularies and guidelines.

Service providers, sites and academic researchers: It is important to involve them to ensure IMPACT can conduct the studies. This includes both trial vendors (predominantly CROs) who will support set-up of GCTCA and the trial centres and academic researchers themselves who will support and conduct the research.

Important to maintain as supporters are the government guardians of public health and the many charities involved in Antimicrobial Resistance (AMR) research, which underpins the need for new antibiotics and, through stewardship, better use of them. IMPACT must also be connected with academics and researchers who are also developing novel approaches to clinical trials, not just for antimicrobials but for other therapeutic areas as well. The IMPACT team must be alert to, and communicate with, parallel researchers.

Finally, but far from least important, are patients who are a critical part of the process, both those participating in the trials and those ultimately receiving the medication. Ultimately, the innovations will deliver new, life-saving products to these patients. In particular, paediatric studies conducted by IMPACT could bring needed antibiotics to children much earlier.

Key IMPACT stakeholders are shown in Figure 4:

Figure 4: IMPACT stakeholders

CRO: contract research organisation; HTA: health technology assessment; IMPACT: International Master Protocol Alliance Clinical Trial

2.2 Pharma and Regulatory Stakeholder Feedback

IMPACT methodology has been reviewed by and discussed with a number of potential collaborating Sponsors, including both large and small pharma with or without the Global Antibiotic Research & Development Partnership (GARDP), BARDA, CARB-X partnership or grants. The interviewed companies have a range of drugs in different phases of development and are mainly based in the EU and the US and were questioned in structured interviews.

Extensive discussions with the FDA and the European Medicines Agency (EMA) also took place.

2.2.1 IMPACT Perceived Strengths and Opportunities

Pharmaceutical companies

All companies showed interest in IMPACT and thought in principle it was valuable.

- **Comments on IMPACT - CCT Methodology and GCTCA Network**
    - **Speed of study start-up and execution** - the conduct of clinical trials:
    - Trials that are conventionally slow to conduct would be completed faster.
    - All trial sites would already be open at the start of the trial.
    - The need for fewer patients to be recruited would speed up trial completion.

    - **Cost** -clinical trials could become more affordable for:
    - First indication allowing faster regulatory approval and market entry.
    - Follow-on indications that Sponsors otherwise may not be able to study and get licensed.
    - Paediatric studies, a regulatory commitment that often has high financial and personnel costs.

    - **Quality and Standardisation** - advantages of training sites to be used continuously:
    - Core set of well-trained trial co-ordinators.
    - Standard understanding of the master clinical trial protocols.
    - Consistency of microbiology specimen collection and handling.
    - Quality of pharmacokinetic assessments.
    - Ability of trial units to recruit for more than one indication.

- **IMPACT - other opportunities:**
    - IMPACT would be a unique Push and Pull initiative for Sponsors.
    - IMPACT could offer a valuable research tool to collect data on patients not enrolled in the primary trials. In particular, the research apparatus could efficiently collect data on the rare cases of infection due to multi- or extensively drug resistant (MDR/XDR) pathogens that will occur across the study sites.
    - IMPACT (GCTCA or methodology) could be also be used for non-standard antibiotics.
    - IMPACT methodology could be used in other therapeutic areas.
    - IMPACT would fulfil an important societal benefit role (e.g. facilitating development of antibiotics for the most relevant indications/populations, improving the quality of data generated by global trial networks, generating information for antibiotic stewardship).

Regulators - EMA and FDA

IMPACT methodology was discussed in face-to-face meetings with EMA and FDA.

- Both agencies recognised the value of getting drugs to the market faster, and the potential for Push and Pull incentives to encourage companies to come to the market with new indications vital to medical need.
- Agencies saw IMPACT CCT methodology generating a valuable source of control group data. This could shed considerable light on populations of patients that enter clinical trials both in terms of efficacy and safety.
- Utilising a GCTCA would mean that patients in the different test agent groups would be enrolled at the same sites, which would reduce the variability caused by CROs generally using a great variety of sites and investigators for the different studies.
- The agencies also considered that there would be extra value if there were some way that the IMPACT trials could identify (e.g. via a parallel sub-study mechanism) MDR/XDR groups of pathogens.

2.2.2 Points to Consider About the IMPACT Set-up

Pharmaceutical Companies

- Positioning the trials - in which indications and at what stage:
    - While some companies considered pivotal studies leading to the first licensing (usually being a cUTI for Gram-negative antibiotics) as less attractive due to the commercial sensitivities and relative ease of recruitment, others indicated that IMPACT support for such studies would be of significant value, especially for smaller companies which would be able to bring their products to the market faster and potentially also invest in the development of additional products.
    - The attractiveness of IMPACT providing support to pivotal studies for follow-on indications (e.g. HAP/VAP) depended on the size of the companies and their ability to at least partially fund such expensive studies. Big pharma companies were highly interested in the conduct of HAP/VAP studies, while biotech companies have expressed concerns regarding their ability to invest in such trials, even with support provided by IMPACT.
    - There was a universal agreement that IMPACT support to paediatric programmes would be of high value for the industry, as paediatric studies are extremely expensive and difficult to conduct, thus diverting the limited budgets and human resources away from the pivotal trials.
- CCT Methodology and Study Design:
    - While there was a general understanding of the basic principles of the CCT methodology, some interviewees found the concept of Non-concurrent Controls complex, indicating a need for more discussion around this particular aspect of study design.
    - The comparator as standard-of-care (SOC) across different geographies needs to be standardised.
    - The protocol needs to allow variability in the inclusion/exclusion criteria so that differing characteristics of individual drugs can be encompassed.
    - The newer drugs with extended spectrum of activity would need to be accounted for and this may require a change in the control SOC.
    - Will there be the ability to allow addition of different antibiotics to cover more resistant pathogens?
    - How cofounding factors (such as the varying renal function) would be managed both within and between patients?
    - Sponsors would like to collect information on some MDR pathogens, for regulatory and commercial reasons.
- Implementation of the study:
    - Each GCTCA unit would need to be able to enrol a minimum number of patients for the trial.

- Data collected must be of highest quality and sites monitored professionally.
- Could IMPACT sustain a Clinical Trial Alliance unit on its own? It could be a valuable resource for conducting other clinical trials. This could extend the utilisation of the network making it more sustainable.
- The number of sites would need to reach a critical mass and have a strong geographic reach to capture the appropriate variability of patients.
- Enough sites should be open at the time of entering the first test agent to allow rapid recruitment.
- Interference by IMPACT CRO and various sponsors in protocol design/preparation may delay the start of the study.
- Will the test agent of one company slow down recruitment for test agent of another, cancelling out the speed advantage?
- Will the study be monitored by a professional CRO?
- The network must be sustainable and funded at a suitable level to ensure the trials can be completed.

- Ownership of data:
  - Concern was raised over loss of control of the data. How flexible it will be, so it can be used for submissions etc., was considered important.
  - Data must be accessible and transferable (no strings attached) if company out-licenses or partners their product.
  - Publication of data would need to be carefully managed.
- Acceptance of the IMPACT methodology:
  - Will regulators accept the CCT approach, especially if Non-concurrent Controls were to be used?
  - Will big pharma accept this approach for smaller companies that may wish to attract a large pharma as a partner for their product development?
  - Will clinicians, HTA agencies and formulary committees accept the data that has come through the network, especially if Non-concurrent Controls were to be included?

EMA and FDA

- Positioning the trials - in which indications and at what stage?
  - Both agencies were generally open to the different indications, but saw particular benefit of IMPACT in the facilitation of the paediatric programmes.
- CCT Methodology and Study Design:
  - Both agencies had reservations about the use of Non-concurrent Controls in pivotal studies. EMA felt these may be overcome, especially if positioned as supportive data for additional indications. FDA were more amenable to shared Concurrent Controls as an initial approach and suggested that the feasibility of using Non-concurrent Controls is evaluated using statistical analyses/modelling of data generated from trials using Concurrent Controls, as well as in workshops with key stakeholders. This could be done in parallel to the IMPACT adaptive CCT design studies.
  - The comparator as SOC had been discussed and this is, in principle, acceptable, as long as the control can be changed from time to time.
  - Both agencies indicated a number of detailed analytical issues that would need to be resolved around how the CCT methodology might be used, especially for the non-concurrent CCT.
  - Both agencies have offered time to work through the different issues.
  - Both agencies felt that IMPACT would offer an opportunity to identify MDR/XDR pathogens.

- Implementation of the study:
    - Site considerations were not discussed in detail and generally they would be the same as for other studies.
- Data:
    - Concern was raised over repeated use of data, especially if published (peer reviewed journals, summary basis of approvals or European public assessment report). Careful management of the reuse of data should be taken into consideration.

3 Prioritised IMPACT Trials and Their Benefits

After extensive consultation with the key stakeholders, three potential IMPACT programmes have been identified: adult cUTI study, adult HAP/VAP study and paediatric study(ies).

3.1 Value of Complicated Urinary Tract Infection in Adult Patients:

- For some Sponsors, mainly smaller pharma (and their government/private funders) without sufficient funds allowing them to progress their development programmes to registration, IMPACT support for a study in adult patients with cUTI would offer a reduced cost and expedited initial approval and market entry.
- A cUTI study in adults would require lower level of funding than a HAP/VAP study and may be more easily funded through Push incentive funding.
- Enrolment into the study will be easier and the study will complete more quickly than for a HAP/VAP study allowing new agents to enter the market and provide benefits to patients earlier.
- As Phase 2 studies for Gram-negative agents are usually conducted in patients with cUTI, there would be a possibility of setting up an adaptive Phase 2/3 study, offering additional advantages in terms of cost and timelines.
- Set up of a clinical trial network for cUTI study would be easier, expediting the IMPACT programme.

3.2 Value of Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia in Adult Patients:

- HAP/VAP is an indication with a high, largely unmet, medical need but clinical trials are complex, and it is difficult to enrol patients into such studies.
- HAP/VAP studies are often not done at all, as companies frequently choose to use only their cUTI (for Gram-negative agents) or acute bacterial skin and skin structure infection (ABSSSI, for Gram-positive agents) trials for market entry and do not have sufficient budgets needed to expand into this indication post-marketing.
- A clinical trial network dedicated to conducting HAP/VAP studies with the ability to incorporate test agents quickly and at a reduced overall cost would benefit sponsors and public health by allowing new drugs to gain approval in this important indication.
- HAP/VAP patient population and the robust endpoints used in the HAP/VAP study design would best support evaluation of the Non-concurrent Controls, providing further advantages to the IMPACT model in the future.

3.3 Studies in Paediatric Patients:

- All antibacterial agents, once approved, must complete a paediatric development plan and for this reason, there is a large number of companies requiring support in this area.
- Because studies in children are focused on safety and pharmacokinetics (PK) and efficacy is not pivotal to regulatory acceptance, there is no commercial sensitivity that would prevent companies from participating in the programme.
- Such a design would reduce the number of children exposed to blood sampling for PK and speed up development of antibiotics for this important patient population.
- The IMPACT initiative offers an advantage to sponsors as they could initiate a paediatric study quickly without the normal effort, time and cost required, and would be able to focus their, often limited, resources on pivotal programmes for new products.

4 Pipeline/Market

4.1 Revenue Sources and Funding for IMPACT

It is intended that IMPACT will be a non-for-profit organisation.

Funding will be provided by pharma clients, government and private funding bodies/organisations. It is anticipated that one to two Sponsors at any one time could participate in the cUTI and HAP/VAP adult studies and two to three in the initial paediatric study. It is assumed that Sponsors participating in the cUTI study would be those with products in Phase 1 or Phase 2 development, while the HAP/VAP study would be positioned for those Sponsors who already have a license for another indication. While it is envisioned that the initial paediatric study would be conducted in children with cUTI, alternative approaches (e.g. single dose PK study across various indications) could be considered. Therefore, the target for participating Sponsors for adult and paediatric studies starting in the next two years are those products which are currently in Phase 1-2 or have recently achieved a New Drug Application or Marketing Authorisation Application for another indication (e.g. cUTI or ABSSSI).

4.2 Market Size

4.2.1 Forecasting for Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia Study

Many compounds can be studied in treatment of HAP and VAP. Relatively few compounds have been studied recently, apart from Zerbaxa and Avycaz (VAP), however some of those that are in the pipeline are for rare MDR or XDR pathogens and may not be suitable to put through the adaptive CCT methodology. Such discussions would need to be held with Sponsors and regulators to understand the best way of approaching such trials. Potential compounds are listed in Table 2.

Table 2: Possible G+ve and/or G-ve antibiotics for study in HAP/VAP

HAP/VAP Study			
2020		**2021-23**	
n = 10		**n = 10**	
Company	**Product**	**Company**	**Product**
Achaogen	Plazomycin	Contrafect	G +ve Lysin
Basilea	Ceftobiprole	Debiopharm	Fabi
Iterum	Sulopenem	Merck	Imipenem+Cilastatin/Relebactam**
Melinta	Vabomere (meropenem/vaborbactam)	Wockhardt	Levonadifloxacin
Merck	Zerbaxa (ceftolozane and tazobactam) *	Allecra	Cefepime/AAI101
Merck	Tedezolid**	Shionogi	cefidercol
Paratek	Omadacycline	Polyphor	Muperavidin
Dong Wa	Zobofloxacin	TaiGen	Nemonoxacin
Tetraphase	Xerava (eravacycline)	Wockhardt	Nafithromycin
R-Pharm	Cefilavacin	Novartis	Monobactam

*Zerbaxa has a VAP study running; ** Tedezolid and Imipenem+Cilastatin/Relebactam have a HAP study running;
G. -ve: Gram-negative; G. +ve: Gram-positive; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia

4.2.2 Forecasting for Complicated Urinary Tract Infection Paediatric Study

A number of compounds have recently been licensed for Gram negative indications. These products will need to complete their required paediatric studies. These are listed in Table 3.

Table 3: Gram -ve antibiotics licensed by end 2020 that will require a paediatric study

Paediatric UTI study			
2019		2020/21	
n = 5		n = 5	
Company	**Product**	**Company**	**Product**
Achaogen	Zemdri (plazomicin)	Iterum	Sulopenem
Melinta	Vabomere (meropenem/vaborbactam)	Shionogi	Cefiderocol
Pfizer	Avycaz (ceftazidime/avibactam)	Merck	Imipenem+Cilastatin/Relebactam
Merck	Zerbaxa (ceftolozane/tazobactam)	Allecra	Cefepime/AAI101
Tetraphase	Xerava (eravacycline)	Pfizer	Avibactam/aztreonam

UTI: urinary tract infection

A number of compounds have also recently been licensed for Gram-positive indications including an ABSSSI study and will need to complete their required paediatric studies. These are listed in Table 4.

Table 4: G+ve antibiotics licensed by end 2020 that will require paediatric study

Paediatric CABP/ABSSSI study			
2019		2020 /2021	
n = 4		n = 6	
Company	**Product**	**Company**	**Product**
Basilea	Zeftera (ceftobiprole)	Motif	Iclaprim
Melinta	Orbactiv (oritavancin)	Nabriva	Lefamulin
Paratek	Omadacycline	R-Pharm	Cefilavacin
		MicuRx	Oxazolidinone
		Cempra	Fusidic acid (Taksta)

ABSSSI: acute bacterial skin and skin structure infection; CABP: community-acquired bacterial pneumonia; G+ve: Gram-positive

4.2.3 Forecasting for Complicated Urinary Tract Infection Adult Study and Long-Term Pipeline

Many compounds nearing clinical development or currently undergoing Phase 1 studies could potentially enter the IMPACT adult cUTI programme. From 2021 onwards, calculations can be made on the pipeline of products using probabilities. However, the most recent pipeline probability information used to assess this for antibiotics is 2014 (O'Neill 2014), which pre-dates new regulatory guidelines. Figure 5 shows the antibiotic pipeline in discovery, preclinical development, Phases 1, 2 and 3 and in registration in 2018.

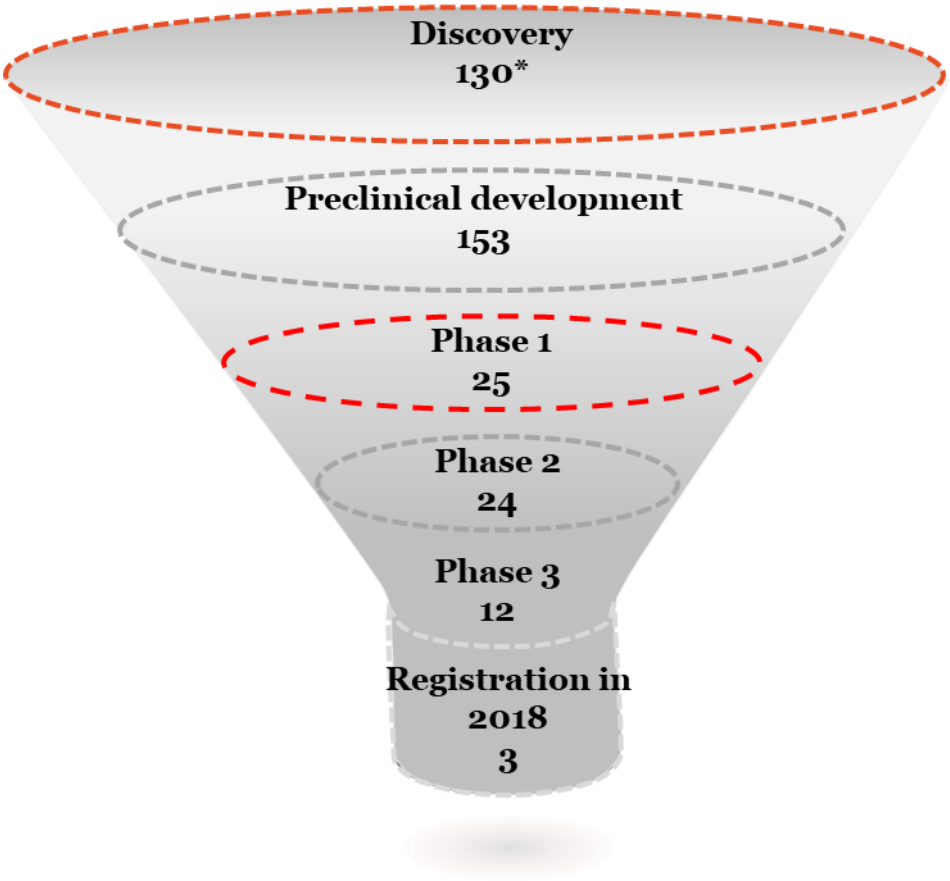

Figure 5: Antibiotic pipeline in discovery

*In discovery compounds may be platforms or programmes:
Products in registration period in 2018 include plazomicin, omadacycline and eravacycline
Source: Global data and (The Pew Charitable Trusts 2018)

It is therefore believed there are a large number of antibiotic technologies in the pipeline which are adequate to encourage 1-2 antibiotics per year through the trial centres for the two prioritised adult indications.

5 IMPACT Management and Organisation

5.1 Organisational Structure

IMPACT will consist of a corporate organisation and three operational divisions, which are:

- IMPACT GCTCA - site management and training division
- Protocol Development, Implementation and Oversight (IMPACT ProDIO) - implementation of individual protocols division, and
- Digital Management and Data Handling (IMPACT DIGITAL) - digital platforms and data management division.

The corporate organisation will be headed by the Chief Executive Officer (CEO) supported by an Executive Assistant. Each of the three divisions will be headed up by a senior manager within the corporate organisation who will provide complete vendor oversight and governance, and who will report directly to the CEO. Beneath each of these division heads, there will be supportive staff as illustrated in Figure 6. Other corporate functions that will report directly to the CEO will include the Head of Project Management, Head of Quality, Finance Director and the Head of Business Development, Public Relations and Marketing.

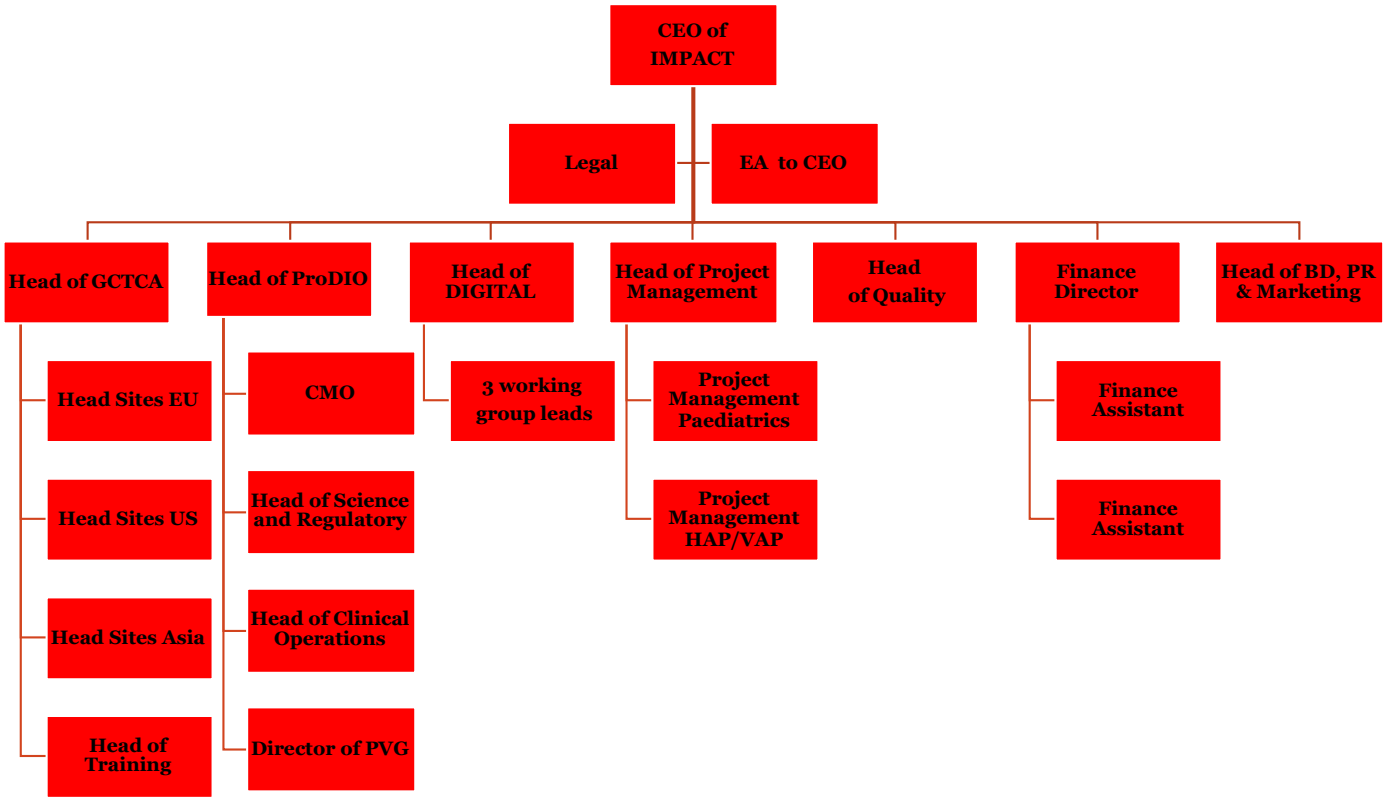

Figure 6: IMPACT organisational structure

BD: business development; CEO: chief executive officer; CMO: chief medical officer; EU: European Union; GCTCA: Global Clinical Trial Centre Alliance; HAP: hospital-acquired pneumonia; IMPACT: International Master Protocol Alliance Clinical Trial; PR: public relation; PVG: pharmacovigilance; US: United States; VAP: ventilator-associated pneumonia

In the following Sections 5.1.1 to 5.1.4, the key process areas (work streams) of the corporate organisation and each of the key three divisions are outlined.

5.1.1 IMPACT Corporate Organisation

IMPACT will act as a Sponsor for the control group and therefore must have an organisation that is compliant with all elements of GCP. The corporate organisation will thus provide overall management and oversight of IMPACT, which will be achieved via the following functions/activities:

- Head of GCTCA, and their direct reports, Head of US sites, Head of EU sites, Head of Asian sites and Head of Training, who will provide oversight and governance of investigator sites.
- Head of ProDIO, and their direct reports, Chief Medical Officer (CMO), Chief Scientific Officer (CSO), Head of Clinical Operations and Director of Pharmacovigilance, will be responsible for the continuous development of the science driving the adaptive design methodology of IMPACT, adaptation of protocols and general governance. In addition, the Head of ProDIO, with the assistance of the Project Managers, will be responsible for vendor negotiations and complete operational oversight (i.e. the highest discount for long term projects).
- Head of DIGITAL and their three working group lead reports will have complete vendor oversight of data handling, digital management, electronic data capture and various e-innovations needed for trial completion.
- Head of Project Management, and their direct reports, Head of Project Management for Paediatric studies and Head of Project Management for Adult studies, who will be responsible for the management of organisational set-up and continuous operational support, as required.
- Head of Quality who will be responsible for ensuring the highest quality output of all IMPACT activities is maintained and for organising audits and inspections as required.
- Finance Director, and two Finance Assistants, will be responsible for monitoring and controlling capital, resource allocation, and time/hours reporting.
- Head of Business Development, Public Relations and Marketing who will oversee the set-up of business relations with decision makers of prospective clients.

Additionally

- Human Resource (HR) Manager (outsourced) will be responsible for all administrative HR processes, performance management, and recruitment.
- Director of Legal (outsourced) will be responsible for contracts, contract lifecycle management, and provides legal counsel.

5.1.2 IMPACT Global Clinical Trial Centre Alliance

The GCTCA division will consist of the Head of GCTCA and their four direct reports, all of whom will reside within the corporate organisation and the subcontracted vendor(s) who will perform the operational activities.

The GCTCA division will focus on 5 key process areas:

- **Alliance Development**: Identification, selection, and qualification of investigational sites; tracking of epidemiological and resistance profiles of sites.
- **Site Contracting**: Negotiation of confidentiality disclosure agreement and Charter Agreements, budget and payment schedules, handling of investigator and site payments
- **Site Engagement**: Relationship management, query resolution, site education (Scope of Alliance network – present and future).
- **Centre of Excellence for Antibiotics Study Start-up**: Training on skills and special software to collect and develop knowledge and templates for local Ethics Committee (EC)/Institutional Review Board (IRB) and Clinical Trial Application (CTA) admissions.
- **Clinical Trial Unit and Site Development**: Identification and communication of site best practices/areas for improvement, target and timeline setting for site development, advisory services.

5.1.3 IMPACT ProDIO

The ProDIO division will consist of the Head of ProDIO and their direct reports (CMO, CSO, Head of Clinical Operations and Director of Pharmacovigilance), all of whom will reside within the corporate organisation, and the subcontracted vendor(s) who will perform the operational activities.

ProDIO will focus on 8 key process areas:

- **Protocol Development**: Development, review and approval of protocols, protocol distribution to sites, sample size calculations, statistical methodology design, biostatistics.
- **Trial Set-up/Trial Monitoring/Governance**: Project management and administrative support, Case Report Form, Informed Consent and other documents, critical document collection, Investigator Meetings, trial monitoring and site management.
- **Regulatory Processes:** IRB/EC submissions, CTA processes, regulatory oversight.
- **Safety and Pharmacovigilance:** Safety oversight, serious adverse event (SAE) management plan, SAE processing and reconciliation, safety reports, SAE database, submission of SAEs to regulatory authorities, SAE narratives.
- **Communication (Sponsors, Investigators):** Educational events (summits, conferences, workshops, etc.), reactive query response, communication of trial pipeline.
- **Trial supplies/central and local laboratories**: Clinical trial materials, management and oversight of supply needs, forecasting of supply needs (based on site profiles and historical trial data), management of laboratory relationships, logistical oversight.
- **Compliance/Audit:** Compliance review of all adaptive trials, quality assurance audit of clinical database (quality management shown separately on the organisation chart).
- **Vendor Management (as required):** Vendor selection, vendor performance review and management, vendor contract management.

5.1.4 IMPACT DIGITAL

The DIGITAL division will consist of the Head of DIGITAL, their three working group lead reports, all of whom will reside within the corporate organisation, and the subcontracted vendor(s) who will perform the operational activities.

IMPACT Digital will focus on 3 key process areas:

- **Data Management**: Data management plan, database design, electronic data capture (EDC) user account management and training, database validation and database lock, programme and quality control edit checks, query management, statistical support.
- **Online Platform**: Online platforms for: site engagement, client query resolution, pipeline/trial overview, best practice sharing.
- **eInnovation**: Innovative Approaches to Trial Conduct.

5.2 Governance Structure

The Heads of the 3 operational divisions and the CEO will form the IMPACT Management Board. It is envisioned that Management Board will have an Advisory Board that would comprise of funding partners and scientific leaders within antibiotics research and development.

6 *Antibiotic Development Collaborations and Consortia*

The GCTCA intends to develop networks of high standard clinical trial sites, which will reduce the risk of trial or programme failure. This will be achieved through initial and continual training to ensure each trial site becomes highly skilled, knowledgeable and efficient. Wherever possible, it is intended that these networks will be set up in collaboration with and building on the experience of many currently existing trial unit alliances. While these existing initiatives fulfil an important role in the fight against bacterial resistance and facilitate development of new therapies, they have not implemented novel clinical trial methodologies that would allow multiple sponsors to come together and streamline their drug development efforts. There is a need for a more collaborative approach to the conduct of clinical trials which would offer significant efficiencies to drug developers and expedite clinical programmes for new antibacterial agents.

Potential collaborators with IMPACT include:

- **IMI COMBACTE:** a pan-European clinical trial network of 933 hospitals and 671 diagnostic laboratories funded by the European Federation of Pharmaceutical Industries and Associations (EFPIA) members and the EU commission which fosters private-public partnerships between Academia, small and medium-sized enterprises and EFPIA members. IMI COMBACTE's objective is to find and develop antibiotics aimed primarily at MDR pathogens.
- **The South East Asia Infectious Disease Clinical Research Network (SEAICRN):** a collaborative network of hospitals and research institutes formed in 2008. The network is financed by the National Institute of Allergy and Infectious Diseases (NIAID) and the Wellcome Trust and in-kind support from local governments.
- **Antibacterial Resistance Leadership Group (ARLG):** launched by NIAID in 2013 as a major effort to combat the public health threat from antibacterial resistance, it focusses on four key areas: Gram-negative bacterial infections, Gram-positive bacterial infections, Stewardship and Diagnostics. Currently, there are 29 studies in progress across all focus areas.
- **Paediatric European Network for the Treatment of AIDS and Infectious Diseases(PENTA-ID):** initiated in 1991 to conduct clinical trials on antiretroviral therapy among HIV-infected children but expanding into other paediatric infectious diseases in 2011, this network spans over 90 clinical sites in 18 countries and is recognised as a Level 1 network for Paediatric Infectious Disease in Europe by the EMA.
- **Global Antibiotic Research & Development Partnership (GARDP):** a joint initiative of the Drugs for Neglected Diseases Initiative (DNDi) https://www.dndi.org/ and the World Health Organisation (WHO) launched in 2016 and aiming to develop and deliver new treatments for existing and emerging drug resistant bacterial infections and where inadequate treatment exists. GARDP is financially supported by Bill & Melinda Gates Foundation and Médecins Sans Frontières amongst others.

7 Implementation of IMPACT

7.1 Overview of IMPACT Implementation

The ultimate goal of IMPACT is to facilitate antibiotic development by implementing a novel way of conducting clinical trials, which will reduce the size and cost of regulatory enabling adult and paediatric studies.

Whilst the exact timing for the roll-out and implementation of the different studies is difficult to foresee at this stage of IMPACT set-up, it is possible that the paediatric programme would be the first to be launched, due to lower complexity of the study design and easier set-up the paediatric GCTCA that is envisioned to be predominantly based on existing paediatric networks. The cUTI and HAP/VAP studies could be launched concomitantly or in a staggered way, depending on the level of interest from pharma companies as well as the available funds. For the purposes of the Business Plan assumptions have been made for draft costing which are described in Section 9. The most important of these assumptions is that the initial programme would consist of a paediatric study plus a HAP/VAP study in adults.

Figure 7 presents an example of a staged implementation of the IMPACT programme, with the paediatric being initiated first and followed by roll-out of a HAP/VAP study in adults.

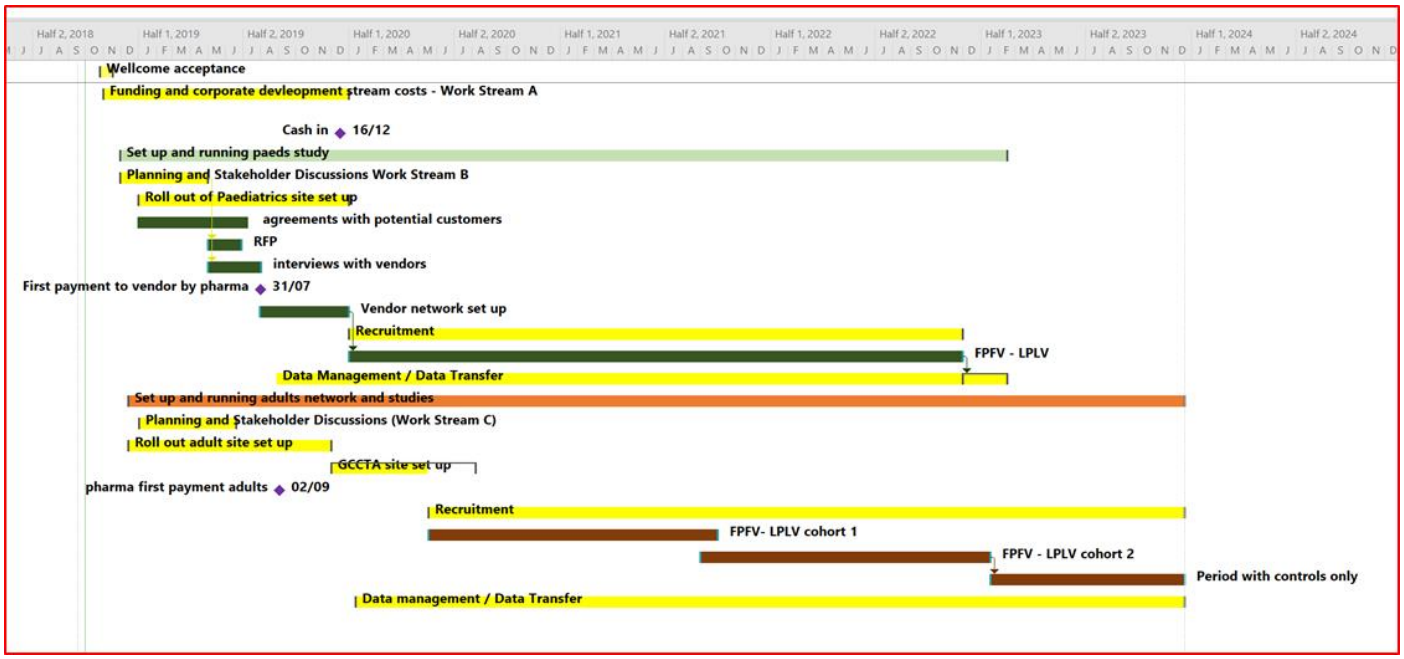

Figure 7: Example of a staged implementation of IMPACT

FPFV: first patient first visit; GCTCA: Global Clinical Trial Centre Alliance; LPLV: last patient last visit; RFP: request for proposal

The key work streams required during the implementation phase of IMPACT include:

- IMPACT corporate recruitment, fund raising and set-up, including initial preparatory activities for the paediatric and adult programmes.
- Set-up of IMPACT paediatric programme.
- Set-up of IMPACT HAP/VAP programme.

IMPACT corporate structure is discussed in more detail in Sections 5 and 9. Set-up of the paediatric and HAP/VAP programmes is presented in the sections below.

7.2 Set-up of the Paediatric Programme

The paediatric programme will be undertaken utilising the standard or adaptive CCT design (as described in Section 1.2.1), depending on the readiness of the participating Sponsors to initiate enrolment at the same

time. Workshops with the participating companies will be organised to discuss and agree the key study design elements.

The objective of this programme is not only to reduce the number of patients needed to complete the study and therefore speed up development of antibiotics for this important patient population but also to reduce the number of children exposed to blood sampling for PK. Normal paediatric trials would recruit approximately 50 patients to each of two groups, one receiving control and one active treatment. For three antibiotics this would require 300 subjects. Paediatric studies are also expensive, can take 4-5 years to complete and occupy resources that could otherwise be used in other clinical development activities for new compounds. In the proposed CCT design, by sharing the control group across three antibiotics, the number of children involved could be reduced to 50 controls and 50 in each of the test agent groups, resulting in a total of 200 patients rather than 300. Utilising the IMPACT GCTCA may have further advantages though efficiencies related to the collaborative approach utilising sites already set up and also an increase in recruitment rates.

The programme will involve development of a smaller, paediatric Clinical Trial Alliance in Europe and the US (potentially based on existing paediatric networks), and the implementation of a paediatric study in patients with cUTIs. An alternative approach for the study could be considered, whereby an adaptive design could combine the required single dose, PK study into the main paediatric study. Additionally, the programme could also include a range of other infections rather than only cUTI.

The study costed in the Business Plan assumes three Sponsors would collaborate in a 4-arm, randomised, controlled study in which patients are randomly allocated to receive one of three test agents or SOC according to a master protocol. It is anticipated that this study will run for approximately 2 years.

7.3 Set-up of a Hospital-Acquired Pneumonia/Ventilator-Associated Pneumonia Programme

It is anticipated that a HAP/VAP programme would be undertaken utilising the adaptive CCT design (as described in Section 1.2.1). For illustrative purposes, this section plus Section 9 will focus on an initial paediatric & HAP/VAP programme. The modelling for a cUTI programme would be similar to that for HAP/VAP. It would also be possible to implement both if sufficient funding were available. A series of workshops will explore the methodological aspects of the adaptive CCT before implementation to address statistical and operational elements. At the same time the development of the GCTCA sites for HAP/VAP will be undertaken. While the units involved in the adult programme may or may not be suitable for inclusion in the paediatric network, there are obvious advantages to the inclusion of centres that can participate in both adult and paediatric studies, and this will be taken into consideration during the site selection process.

When the adaptive CCT methodology has been agreed and a suitable GCTCA established, a study in patients with HAP/VAP would be undertaken.

7.4 Further Stakeholder Discussions

It is anticipated that further stakeholder discussions to gain full regulatory authority endorsement of the IMPACT methodology will be required before kick-off of the selected studies.

The following key stakeholders will be consulted (others may also be included):

- Sponsors (big pharma and biotech and/or funding partners).
- Regulators (FDA and EMA).
- Trial sites and potentially collaborating networks.
- Academic institutions.
- CROs.

- Funding bodies (e.g. BARDA).

8 *Positioning of IMPACT in the Antimicrobial Resistance Ecosystem*

Positioning IMPACT's offering is critical to ensure that IMPACT achieves its public health goals, maximises the opportunity it is trying to create and ensures sustainability. The objective of the positioning statement is to internally align on the essence of the offering and to communicate with one voice to the external stakeholder community. The positioning statement, therefore, needs to state a) the stakeholders who benefit, b) how IMPACT distinguishes itself from all the other Push, Pull and collaborative initiatives, and c) how the participants will benefit from IMPACT's features.

FOR Sponsors, their funders/investors/stakeholders who are developing innovative antibiotics for the treatment of serious infections to provide badly needed antibiotics sooner for the benefit of public health.
IMPACT is a ground-breaking new collaborative model for conducting clinical studies, utilising an adaptive CCT design of continuously active, high quality clinical trial centres.
THAT

a) Increases SPEED of trial completion
b) Increases trial QUALITY
c) Reduces overall COST of clinical trial execution
d) Improves antibiotic KNOWLEDGE.

BECAUSE

a) IMPACT offers an FDA- and EMA- acceptable adaptive CCT methodology, sharing control subjects and clinical trial costs between Sponsors, thus reducing the size and cost of the studies to be borne by individual Sponsors
b) IMPACT will work with qualified and highly trained trial centres and ensure continuously running clinical trial network thereby
    - Reducing the study start up time and cost to a minimum as sites only require the approval of protocol, with most sites being ready to quickly incorporate a new drug into their already ongoing enrolment momentum
    - Significantly reducing the time of enrolment as sites all start at once and continuously enrol into the master protocol
    - Improving the quality of data, due to intensive training system of selected trial centres which are continuously running
    - Offering best in class high quality oversight, study management, data management and innovative techniques
    - Broadening the number of well-trained research sites globally.

SO THAT Sponsors have a faster, more reliable trial execution and can shift management attention and resources to other areas of clinical development of antibiotics, while the regulators, clinicians and public health benefit from robust research and education to effectively fight antimicrobial resistance.

9 Example Financial Plans and Funding Requirements

IMPACT will be set up with an organisational structure and professional contracted services. Therefore, the cost structure is separated into people requirements and long-term contracted services.

The total cost savings will depend on the selected combination of studies, sponsors, and agents. As an example, the following section estimates costs for a 3-drug pediatric study (simultaneous start) plus a two-agent HAP/VAP study (staggered start).

9.1 People and IMPACT Requirements

Fully loaded full-time equivalent (FTE) costs are currently estimated to range between $65,000 and $350,000 (US) per FTE, depending on role and level of seniority. A complete list of people requirements by division, including fully loaded annual FTE costs, and current thinking on in-house versus third party resourcing is shown in Table 5.

Table 5: Personnel cost estimate by division and working group.

FTE Information				
Position	**FTE**	**Full Year FTE Costs**	**In House or Vendor**	**Start Date**
CEO Office (total)	**2.0**			
CEO	1.0	$ 350,000	IMPACT	Q3/2019
Executive assistant (EA) & office manager	1.0	$ 65,000	IMPACT	Q3/2019
Project Management (total)	**3.0**			
Head of PM	1.0	$ 200,000	IMPACT	Q3/2019
Head PM (paeds)	1.0	$ 150,000	IMPACT	Q3/2019
Head of PM adults	1.0	$ 150,000	IMPACT	Q4/2019
Finance / Controlling (total)	**2.5**			
Finance Head	0.5	$ 180,000	IMPACT	Q2/2019
Finance assistants	2.0	$ 80,000	IMPACT	Q1/2020
HR (total)	**0.5**			
HR Services	0.5	$ 100,000	Vendor	Q2/2020
Legal (total)	**0.5**			
Legal Services	0.5	$ 180,000	Vendor	Q2/2019
Quality (total)	**1.0**			
Head of Quality	1.0	$ 180,000	IMPACT	Q1/2020
GCTCA (total)	**4.5**			
Head of GCTCA	1.0	$ 200,000	IMPACT	Q2/2020
Heads of EU, US and Asia	3.0	$ 150,000	IMPACT	Q4/2020
Centre of Excellence Head	0.5	$ 150,000	IMPACT	Q4/2020
ProDIO (total)	**5.0**			
Head of ProDIO	1.0	$ 260,000	IMPACT	Q2/2019
Pharmacovigilance	1.0	$ 260,000	IMPACT	Q2/2020
CMO	1.0	$ 350,000	IMPACT	Q2/2019
Head of clinical ops	1.0	$ 200,000	IMPACT	Q3/2019
Head Scientific and Regulatory	1.0	$ 280,000	IMPACT	Q1/2020
BD & Communication	**1.0**			
BD & Communication Services	1.0	$ 210,000	Vendor	Q1/2020
Digital	**4.0**			
Head of DIGITAL	1.0	$ 210,000	IMPACT	Q4/2019
Work group heads	3.0	$ 150,000	IMPACT	Q2/2020

$: US dollars
BD: business development; CMO: Chief Medical Officer; EA: executive assistant; EU: European Union; FTE: full-time equivalent; GCTCA: Global Clinical Trial Centre Alliance; HR: human resource; IMPACT: International Master Protocol Alliance Clinical Trial; Q: quarter; US: United States

9.2 Set-up Cost Assumptions

The following set-up activities have been costed. The actual costs are shown in Section 9.4.

9.2.1 Set-up Phase

Set-up costs are assumed to include the following groups of activities:

- Development of paediatric master protocol and negotiation and set-up of the paediatric site network.
- Development of HAP/VAP master protocol and negotiation and set-up of the HAP/VAP site network.
- Development of cUTI master protocol and negotiation and set-up of the cUTI site network.
- Corporate recruitment, fund raising and set-up of the organisation.

These set-up costs will be the costs at risk to IMPACT.

9.2.2 Paediatric Network and Set-up

- Visits and negotiations with sites and organisations which have paediatric sites with whom IMPACT might collaborate.
- Discussions around the master protocol and visits to FDA, EMA and other interested agencies.
- Discussions with potential and participating companies.
- Identification of potential operational issues and any other issues that have been detected in recent paediatric studies.

9.2.3 Hospital-acquired Pneumonia/Ventilator-associated Pneumonia Set-up

- Visits and negotiations with organisations which have adult sites with whom IMPACT might collaborate.
- Discussions around the master protocol and visits to FDA, EMA and other interested agencies.
- Understanding of potential statistical or analytical issues.
- Discussions with potential participating and participating companies.
- Identification of potential operational issues and any other issues that have been detected in recent HAP/VAP studies.
- Determining next steps for future study designs or innovative technologies (rapid diagnostics, continuous vital sign monitoring etc).

9.2.4 Corporate Recruitment, Fund Raising and Set-up

- Fund raising
    - Interactions with governments and private philanthropists
    - Managing potential funding models for initial set-up
    - Managing and proposing future business model and funding for sustaining the organisation.
- Agreement on how companies are subsidised in terms of match funding agreements or other means of commitments.
- Setting up IMPACT's corporate structure e.g. legal entity, administrative, clinical and operational staffing, corporate branding, etc.
- Setting up internal SOPs, including GCP-related procedures.
- Registering IMPACT as a Not-for-Profit organisation or as a Charity.

9.3 Summary of Cost of the Clinical Trials

Details are presented in the Appendix.

9.3.1 Estimated Savings Criteria

The illustrations below demonstrate savings to Sponsors, using the following colour coding:

- Light grey – CRO costs, the vendor CRO costs which steadily reduce with efficiencies across sites.
- Blue – CRO pass through costs, these are patient-related fees, predominantly investigator and laboratory fees.
- Dark grey – CRO savings due to the efficiencies of collaborative CCT study design
- Orange – additional savings to Sponsors when public and private funders pay for part, or all, of the Control subjects.

9.3.2 Paediatric studies

- Scenario 1 reflects the full conventional cost of an individual study.
- Scenario 2 is based on sponsor collaboration only. It reflects the total cost of three test agents and one control group divided by three. However, significant internal costs for the management of the collaboration are required (not reflected in Figure 8).
- Scenario 3 is based on Scenario 2 but assumes that IMPACT also funds the network establishment and 50% of the control group.
- Scenario 4 is based on Scenario 2 but assumes that IMPACT also funds the network establishment and 100% of the control group.

Figure 8 illustrates the savings to Sponsors for paediatric studies as the collaboration savings occur due to the IMPACT CCT design, and the further costings to sponsors as IMPACT funds the control subjects. It could assumed that an additional CRO discount of approx. 15% would be negotiable for the IMPACT scenarios, due to the longevity of the project (not reflected in Figure 8).

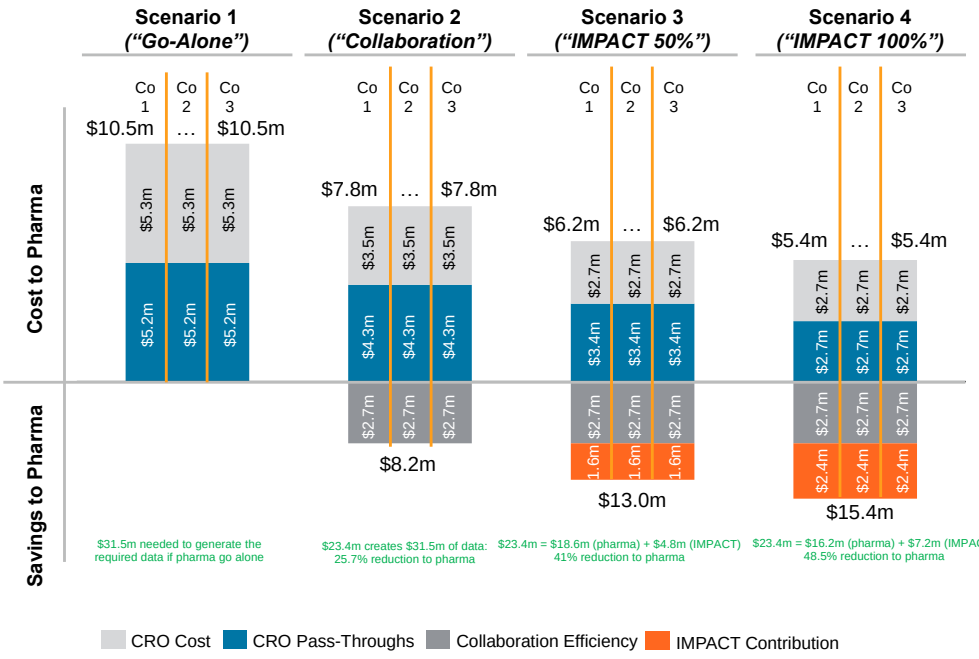

Figure 8: Scenario of sponsor costs of paediatric studies

CRO: contract research organisation; IMPACT: International Master Protocol Alliance Clinical Trial

IMPACT CCT design alone saves the Sponsors 25.7% of study costs. If IMPACT funds 50% or 100% of controls, the savings to the Sponsors are 41% and 48.5%, respectively, not accounting for reduction in vendor contract negotiations or other savings due to IMPACT infrastructure support.

9.3.3 *Hospital-acquired Pneumonia/Ventilator-associated Pneumonia Adult Studies*

- Scenario 1 reflects the full conventional cost of an individual study.
- Scenario 2 is based on sponsor collaboration only. It reflects the total cost of two test agents and one control group. However, significant internal costs for the management of the collaboration are required (not reflected in Figure 9).
- Scenario 3 is based on Scenario 2 but assumes that IMPACT also funds the network establishment and 50% of the control group.
- Scenario 4 is based on Scenario 2 but assumes that IMPACT also funds the network establishment and 100% of the control group.

The assumed scheduling of patient recruitment is shown in Table 6.

Table 6: Scheduling of HAP/VAP cohorts

	2020				2021				2022				2023			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Study 1																
Study 2															*Gap*	*Gap*
Total Patients per Quarter	25	75	105	105	105	105	105	105	105	105	105	105	105	105		
Enrollment Study 1			52.5	52.5	52.5	52.5	35	35	35	35						
Enrollment Study 2							35	35	35	35	52.5	52.5	52.5	52.5		
Enrollment Control Group	25	75	52.5	52.5	52.5	52.5	35	35	35	35	52.5	52.5	52.5	52.5		

HAP: hospital-acquired pneumonia; Q: quarter; VAP: ventilator-associated pneumonia

Figure 9 illustrates the savings to Sponsors for HAP/VAP studies as the collaboration savings occur due to the IMPACT design, and the further costings to sponsors as IMPACT funds the control subjects. It could assumed that an additional CRO discount of approx. 15% would be negotiable for the IMPACT scenarios, due to the longevity of the project (not reflected in Figure 9).

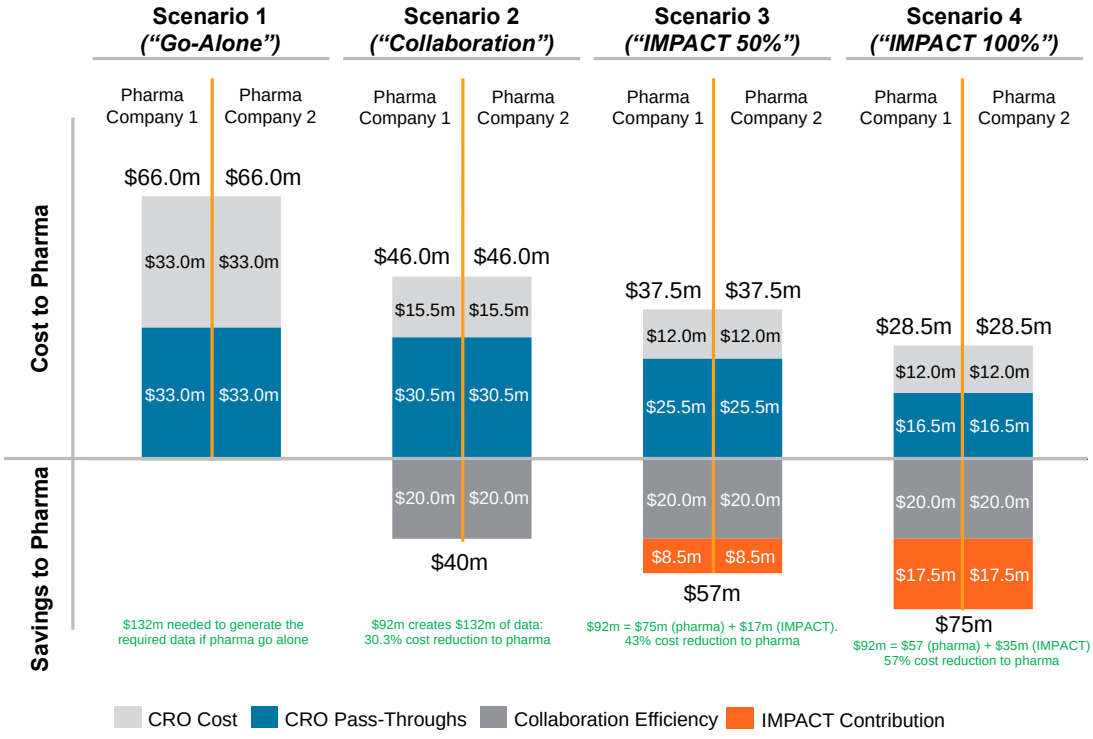

Figure 9: Scenario sponsor costs of HAP/VAP studies

CRO: contract research organisation; HAP: hospital-acquired pneumonia; IMPACT: International Master Protocol Alliance Clinical Trial; VAP: ventilator-associated pneumonia

IMPACT CCT design alone saves the Sponsors 30.3%. If IMPACT funds 50% or 100% of controls the savings to the Sponsors are 43% and 57%, respectively, not accounting for reduction in vendor contract negotiations or other savings due to IMPACT infrastructure support.

9.4 Integrated Summary: Cash Flow and Funding Requirements

Table 7 presents the IMPACT cash flow and funding requirements. It includes all the CRO costs and income from pharma drug Sponsors (paying for their own test agent cost) as well as funding from governmental bodies and philanthropy.

Scenario 4 (100% of funding of controls) has been used for both the paediatric study and HAP/VAP study. Execution of cUTI study(ies) is not reflected within the P&L, but can be seen as additional upside to further cover fixed costs.

The costs include full overhead costs including personnel as described in Section 9.1 as well as office rental, IT, etc. based on real illustrative costs. Set-up costs described in Section 9.2.1 have been included as well.

Table 7: IMPACT cash flow [US$]

	2019	2020	2021	2022	2023	Total
Income received by IMPACT						
Funding from governments and philanthropy	***7,500,000***	***30,000,000***	***16,000,000***	***16,000,000***	***16,000,000***	***85,500,000***
Funding from pharma drug sponsors						
HAP-VAP	*-*	*7,114,000*	*21,336,000*	*21,336,000*	*7,114,000*	*56,900,000*
Paediatrics	*-*	*5,359,000*	*5,359,000*	*5,359,000*	*0*	*16,077,000*
Total	***-***	***12,473,000***	***26,695,000***	***26,695,000***	***7,114,000***	***72,977,000***
Income (Total)	**7,500,000**	**42,473,000**	**42,695,000**	**42,695,000**	**23,114,000**	**158,477,000**
Costs						
CRO Costs	*-*	*27,382,000*	*35,865,000*	*35,865,000*	*12,998,000*	*112,110,000*
Set-Up Workstreams	*820,000*					
Network Set-Up Costs	*1,165,000*	*6,925,000*	*576,000*	*576,000*	*576,000*	*9,818,000*
IMPACT Personnel	*1,887,300*	*6,019,873*	*6,557,918*	*6,535,054*	*6,731,105*	*27,731,250*
Other[1)]	*715,000*	*761,000*	*761,000*	*761,000*	*761,000*	*3,759,000*
Costs (Total)	**4,587,300**	**41,087,873**	**43,759,918**	**43,737,054**	**21,066,105**	**153,418,250**
Income-Costs	**2,912,700**	**1,385,127**	**-1,064,918**	**-1,042,054**	**2,047,895**	
Balance (to provide WC)	**2,912,700**	**4,297,827**	**3,232,909**	**2,190,856**	**4,238,750**	

1) Rent, IT, Insurance, Fees, etc. WC = Working Capital

CRO: contract research organisation; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia

Hypothetical funding from governments and philanthropic organisations has been added to the model. In order to cover a period with no test agents as of Q2/2023, IMPACT would need to raise US$85.5m: $7.5m in 2019, $30m in 2020 and $16m in the years 2021, 2022 and 2023. Reason for an increased funding need in 2020 is the financing of the set-up of the clinical trial network (study start-up activities) and the run-in phase (enrolment of control group patients). The period when there are no test agents increases the administrative cost to IMPACT. Fewer than three test agents in the paediatric study would increase costs for the Sponsors.

Other funding models could be considered where large pharma pay more than smaller pharma, such scenarios have not been modelled in this Business Plan.

9.5 Summary of Cost Savings

In order to estimate the potential overall savings to the total development costs of antibiotics (including Sponsors as well as public and private funders), this Business Plan has tested whether there would still be savings with maximum IMPACT infrastructure in place under a conservative scenario when only one paediatric study (three test agents) and a HAP/VAP adult study (two test agents with staggered start) are run and when no test agents are in the adult trial for 9 months at the end of the adult study, whilst IMPACT maintains the control group. Overheads have been estimated at maximum US salaries, based on Hays data. It has also been assumed that the set-up of the network is fully born by IMPACT with no collaboration with other networks.

Total costs of overheads for five years have been estimated and balanced against the savings offered by the paediatric and HAP/VAP studies, and are presented in Table 8.

This estimation of savings associated with the IMPACT model is agnostic as to whether the funds are received from pharma drug Sponsors or government or philanthropic organisations. As can be seen in Table 8, the operational savings related to the collaborative study design and CRO discount are greater than the cost of setting up and maintaining of the IMPACT organisational structure.

As illustrated in Table 8, with only one paediatric study with three agents and a HAP/VAP trial with two agents, there are still savings in the overall cost of running these trials individually, in spite of the need for IMPACT infrastructure.

Table 8: Savings on collaboration for paediatrics and HAP/VAP, versus cost of IMPACT

Savings and Spend	Value ($ million)
Collaboration Savings	
Paediatric study collaboration	8.2
Paediatric study CRO discount	3.5
HAP/VAP study collaboration	40.1
HAP/VAP study CRO discount	13.8
Total collaboration savings	**65.6**
IMPACT Overhead	
IMPACT network set-up	9.81
IMPACT personnel overheads (5y)	27.731
IMPACT other overhead (5y)	3.759
Total IMPACT overhead	**41.30**
Savings - overhead	**24.3**

Source: Figure 8 and Figure 9 for savings and Table 7 for IMPACT overhead
CRO discount was assumed to equal 15% of the total paediatric and HAP/VAP study budgets. Total study budgets can be calculated by combining the CRO cost, CRO pass-throughs and IMPACT contribution, as presented in Figure 8 and Figure 9 (Scenarios 3 or 4);
The calculation does not take into account additional costs incurred when IMPACT would be the sole Sponsor (no test agents in the trial)
CRO: contract research organisation; HAP: hospital-acquired pneumonia; IMPACT: International Master Protocol Alliance Clinical Trial; VAP: ventilator-associated pneumonia

Another way of assessing the benefits of IMPACT is to look at its benefits to society in terms of the value of scientific data generated by the IMPACT programmes. The social benefits of the IMPACT investment have been assessed by estimating the potential return to the society on an investment into paediatric and adult HAP/VAP programmes, based on IMPACT scenario 4 described above.

Figure 10 summarises the benefits of the IMPACT model applied to the paediatric and adult HAP/VAP programmes. The required governmental and/or philanthropic funding of 85.5 US$ m from 2019 to 2023 as presented in Table 7, together with 73US$ m of pharma Sponsors contribution fuels data generation

worth 163.5 US$m. From the standpoint of the governmental/philanthropic Sponsors and the pharma Sponsors, each group can view IMPACT as having approximately halved the cost of generating these data.

Additionally, IMPACT has created durable value that can be used for further work. There is a residual tangible value of approx. 13 US$ m related to the establishment of IMPACT GCTCA as well as IMPACT Working Capital. This programme base offers the IMPACT organisation as an established and tested global network of highly skilled trial units that will provide additional efficiencies for the next round of paediatric and adult programmes.

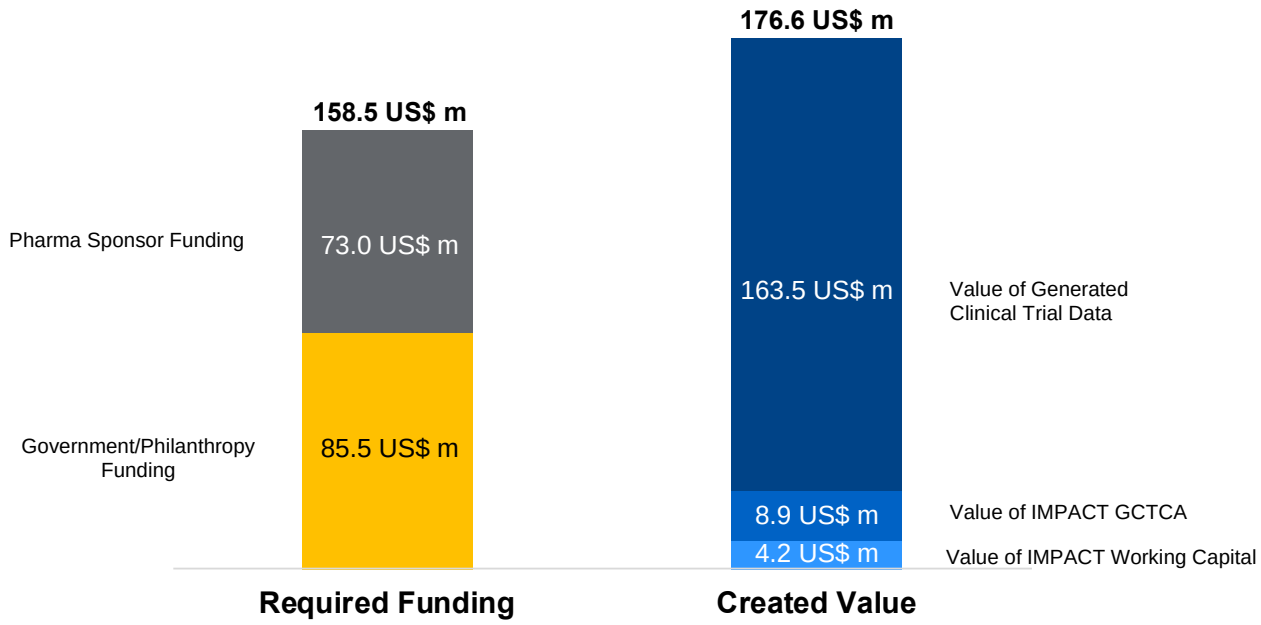

Figure 10: Social return of IMPACT investment

Source: Figure 8, Figure 9 and Table 7
GCTCA: Global Clinical Trial Centre alliance

9.6 Conclusion

In summary, with only one paediatric study with three agents and a HAP/VAP trial with two agents, IMPACT offers substantial savings in the overall cost of running trials individually, providing an important benefit to the society. Whilst there are clear savings associated with the IMPACT study design, there is also a requirement for funding from various sources to ensure the set-up of IMPACT can effectively achieve this.

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