



Clinical Trial Networks for Antibiotic Development:

Why they're important and how
they should be developed.

Written by a multi-stakeholder working group led by
Anthony McDonnell and funded by the Wellcome Trust

Contents

Executive summary	1
Introduction	2
How clinical trial networks could work	4
Clinical trial goals	4
Types of clinical trial network	4
Is demand high enough to sustain a network?	5
Co-ordination problems; why has a network not been established already?	6
Unique advantages	10
Warm base advantages	10
Sharing control groups	13
Potential total financial savings	16
Other advantages	16
Practicalities	19
Data management	19
Consent and institutional review boards	19
Managing entry and exit of investigational drugs	19
Blinding within a continuous master protocol	20
Next steps and research needs	21
Conclusion and overview of working group	24
Acknowledgements	25

Executive summary

The cost and long duration of late stage clinical trials of antibiotics are a significant barrier to bringing new treatments to patients. Between 50 and 300 hospitals must be found and taught the protocol, and then have the infrastructure ready to enrol patients 24 hours a day. It can be hard to find suitable patients: they need to be enrolled very quickly, because bacterial infections progress rapidly, but full diagnoses are often not fast enough. Patients also cannot be moved between hospitals. These problems apply especially to patients with multi-drug-resistant pathogens or rare infections like *Pseudomonas*.

Many different groups have sought to make the trial system more efficient. This would reduce the cost of antibiotic development, making it easier for both public and private institutions to create the drugs we need in the fight against antibiotic-resistant bacteria.

Within this search for efficiencies, there is widespread support for the idea of clinical trial networks, but different views on what they should look like and what a network's primary function should be. In order to move this process forward, 16 of us started a multi-stakeholder working group in early 2016 to examine the benefits and practical issues surrounding clinical trial networks.

Building on the work of trial networks in other areas, we believe that a network could help registrational trials to more quickly and cheaply enrol a large number of patients with usual drug-resistant infections. It could also facilitate parallel follow-on and optimisation studies that seek to enrol patients infected with rarer or drug-resistant organisms. We have examined the number of clinical trials currently taking place that could be put into a network, as well as those going forward that could be, and we believe that there are enough trials underway to sustain a clinical trial network.

We have put forward two different approaches for a network. The first is the Globally Connected Trial Sites system, which would find good trial sites across the world that a sponsor could quickly enrol their drug in. Our initial informal estimate suggests that such a system could potentially reduce the costs of Phase II and Phase III trials by 23 percent. The second approach, a Continuous Master Protocol, would create even greater efficiencies by allowing trials to share control groups, and potentially use control data from previous trials. This could reducing the cost of trials by as much as 40 percent to 60 percent, depending on whether using previous control groups is possible.

In this work, we have taken initial steps to address the practical difficulties that relate to a clinical trial network, but we believe greater research is needed to examine the exact benefits of a network, the logistical issues with establishing one, how the governance could work and where funding for the network could come from. This research will not be expensive and is the logical next step on the way to creating clinical trial networks.

Introduction

Not enough antibiotics are being created to combat the growing level of antibiotic resistance in the world. This is particularly true of antibiotics for infections caused by Gram-negative bacteria¹. This is an increasingly well studied phenomenon that has recently been recognised by the G20 and the UN General Assembly. Increasing the supply of new drugs is one element of the overall programme to manage drug-resistant infections, and improving the drug pipeline itself will require a multifaceted approach.

There are three ways to improve the supply of new antibiotics: increase funding of early-stage research for drugs, make the drug development process more efficient and improve the rewards for those who come up with important new drugs. Each of these probably needs to improve in order to create a healthy antibiotic pipeline². In this paper we focus particularly on how to improve the efficiency of antibiotic development through the creation of clinical trial networks.

At the moment, every time an investigator designs a clinical trial to test a new antibiotic, she must recruit and enrol 50-300 hospitals to test the new drug. This involves not only finding hospitals willing to run the trial, but also negotiating legal and financial terms with each hospital and then training their staff on the protocol. This costs the drug sponsor both time and money, and it can take a while before the hospitals are familiar with the protocol, leading to low productivity in the early months of the trial. Compounding this problem, anecdotal evidence, the authors' experience, and evidence from other types of clinical trials suggest that about 30 percent of hospitals in any given antibiotic clinical trial fail to enrol any patients at all, and many perform less well than they are supposed to; this is despite trial sponsors doing their best to only recruit hospitals that they believe will meet their requirements³. Once the trial is over, the temporary network of hospitals that the sponsor has created disappears and someone conducting future drug research must once again spend a large amount of time and money identifying new hospitals to be part of this process.

Clinical trials relating to different diseases have different requirements. Antibiotic trials are made difficult by the extraordinarily short window in which a patient can be enrolled into the trial. Patients must generally be enrolled into a trial almost immediately (often before there's time to receive results from a full diagnostic workup). In addition, patients with bacterial infections generally cannot be moved from one hospital to another, both because of the time-critical nature of their illness and because there's a risk in some situations that they can pass their infection on to others.

In other diseases, problems with finding patients have been overcome by the establishment of clinical trial networks. For malaria, TB and HIV, large networks have been used to reduce the costs, find patients in remote areas, track resistance and run large trials quickly. For cancer, several networks exist to find patients with rare indications. Many of the networks in existence benefit from the fact that the disease under study runs slowly enough for at least some patients to be referred to a central treatment site, an option that is not open at all to trials of antibiotics.

Despite these challenges, we believed that networks might be designed to significantly help antibiotic drug discoverers to enrol enough patients in a drug trial, 16 of us came together at the beginning of this year and established a working group to discuss how it might be possible to make clinical trial networks work for the challenging antibiotic setting. Between us there are members from government, academia, small and large pharmaceutical companies, patient advocates and regulators (see page 24). As part of the process of writing this paper and socialising our research, we also held a conference in London on the 11th of October 2016, where we sought inputs from people across government, industry, academia and research from a much larger number of countries.

Based on our initial and still somewhat rudimentary analyses, we outline below possible approaches to, and benefits of, antibiotic-focused trial networks. We found that clinical trial networks could reduce the cost of running Phase II, III and IV clinical trials by almost a quarter and that if a network were to use a continuous master protocol and share control groups that this saving could rise to between 40 percent and 60 percent depending on the type of control group sharing that was possible. A network could also significantly reduce the time it takes drug discoverers to run clinical trials.

¹ Outterson et al, *Approval and withdrawal of new antibiotics and other anti-infectives in the U.S., 1980-2009* (2013)

² Review on AMR, *Tackling Drug-Resistant Infections Globally: Final Report And Recommendations* (2016)

³ McDonald et al, *What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies* (2006)

How a network could make clinical trials more efficient

Spend months finding hospitals, signing contracts and creating own grouping of sites

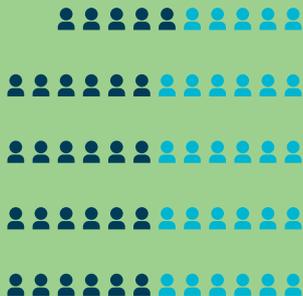


Typically 1/3 hospitals won't enrol any patients

Trial enrolls patients slowly at the start as hospitals and clinicians get used to the protocol.



Half the patients must be assigned to the control group, meaning that more are required which will increase the cost and time of the trial.



Connection between hospitals disappears

Time*

Plug straight into existing network



Network able to enrol patients quickly and reliably as it's well honed.



By sharing control groups with other trials less patients are needed, reducing time and increasing speed.



Network ready for next trial

-  Treatment group
-  Control group
-  Shared control group

How clinical networks could work

Clinical trial goals

There are three types of trials that are generally run for antibiotics and a clinical trial network could help with each type. The first category is that of Phase II and III trials on usual drug-resistant infections (UDR), infections that are susceptible to the standard first-line treatment. These types of studies are the foundational studies used to gain initial registration. These studies usually focus on complicated urinary tract infections (cUTI) or complicated intra-abdominal infections (cIAI), and sometimes hospital-acquired and ventilator-associated bacterial pneumonia (HAP/VAP). If the drug is shown to be both safe and effective in these serious but still reasonably common settings, follow-on studies then often take place in more challenging settings with studies to show efficacy in children, against resistant infections or in other indications. This second category of study types is used to both expand the number of indications the drug can be prescribed for as well as to show clinicians and payers that the drug is worth using. Finally, optimisation studies can be run for some drugs in order to improve dosing and test combinations. This type of research is typically for public benefit rather than for the financial benefit of the sponsor, meaning it is often funded by academia or governments rather than industry.

A network could cover all three types of studies (registration, follow-on and optimisation), but each has unique challenges and characteristics. Phase III studies for registration need to be relatively large in order to provide clear and statistically relevant evidence of efficacy. For the majority of infections, the designs of these trials have become substantially standardised with respect to both case definitions and end points, and so it might be possible to run them with one master protocol, as discussed later. The need to capture a large number of patients in these trials is similar to the aims of some of the malaria trial networks mentioned above.

Some follow-on studies might be large and in UDR indications that have not been tested yet, such as HAP/VAP. For the purposes of a network these can be treated in the same way as registration studies even if they are in fact post-registration as they will still receive a similar level of regulatory review in order to broaden drug labelling. Most other types of follow-on studies aim to find unusual types of patients, such as neonates with sepsis, less common specific organisms (e.g., *Pseudomonas aeruginosa*) or multi-drug-resistant infections. These studies tend to be much smaller than registrational studies, but the patients are much harder to find. The needs of a network for such studies will thus differ considerably from those of a network focused on registration.

Optimisation studies may end up being either large or small and are generally about getting the most out of existing drugs. These studies can be large and on UDR patients, and thus like registrational studies, but are more often small and on a niche group, similar to follow-on studies. While this makes them easier to run alongside the other two types of studies, they are often run by not-for-profit entities, and have sponsors who are under less time pressure, but have greater financial constraints.

Types of clinical trial network

There are several ways to set up a clinical trial network and the working group has considered two major possibilities. We've labelled the first the "Globally Connected Trial Sites" (GCTS) model, which would aim to connect a series of sites so that sponsors can easily come to one if they have a drug they want to test, and can then run the trial as per usual, with each trial having its own individual protocol. The second option is a single global network operated by one entity with a single defined protocol; we have labelled this the "Continuous Master Protocol" (CMP) model.

While each model has its own advantages, a GCTS network will be easier to set up, as it can be built on existing clinical networks and structures. It can also start small and improve its capacity over time.

In comparison, a CMP network will require more time and capital to set up, and will only work for more common indications. But, once it is set up, there can be greater efficiency savings as sites will already be familiar with the protocol when a new drug is entered into a trial, and it should be possible to reduce costs by sharing control groups, as we discuss later.

These two approaches do not have to be mutually exclusive. We think a CMP is best placed to deal with registrational trials, and some optimisation work, whereas if a sponsor wants to go after smaller follow-on studies then a GCTS is the best approach to take. There is no reason why both cannot be included in a network, or that two complementary networks taking each approach can't be set up.

Is demand high enough to sustain a network?

It is widely documented that there is a shortage of new agents coming through the antibiotic pipeline. Indeed, this working group is motivated primarily by a desire to help reduce the shortage of new antibiotics by improving the economic case for investing in antibiotics. This shortage of drugs has quite rightly led many to question whether there are enough antibiotics coming through the pipeline to sustain such a network.

We hope that a fully-functioning network will be able to operate the equivalent of at least one Phase II and one Phase III study in each year for cUTI, cIAI and HAP/VAP. This would require 500

to 1000 patients per annum for cUTI and for cIAI, and 300 to 600 patients per annum for HAP/VAP. In order to determine the prospects for forming such a network, a review of the clinical trials registered on the website ClinicalTrials.gov was conducted, and trials that could have been entered into a network were selected (that is trials on adult populations with UDR infections for cUTI, cIAI and HAP/VAP). The conclusion is that each indication had sufficient patients enrolled in trials in 2012, 2013 and 2014, but in previous years, a network would not have been able to fill each indication.

Estimates of the number of patients in trials that could likely be enrolled into a clinical trial network

	2008	2009	2010	2011	2012	2013	2014	Average
cIAI	26	226	113	194	735	1095	763	450
cUTI	635	714	423	289	674	1374	1533	806
HAP/VAP	561	191	186	735	1494	2361	1751	1040
All Three	1222	1131	722	1219	2903	4831	4047	2296

The above table demonstrates that most years, there are sufficient patients to fill a network for the three indications. This is reassuring. However, the network will need to be flexible enough to deal with the changing numbers of patients that will be received in different years, as demand is likely to vary. At the conference we held, one of the greatest worries from industry was that if too many people subscribed to the network at the same time, everyone's projects would be slowed down. But having multiple companies running trials at the same time on the same indication is going to make finding patients difficult and slow companies down regardless of whether there is a network. Under a network with a master protocol there is the ability to offset this by sharing control groups between the networks. Because drug development is a relatively slow

process, drugs that could benefit from a network will be visible for at least a few years in advance. Meaning that good forward planning should permit pre-emption of any rise in demand for the network so that sponsors don't get slowed down or forced to go outside the network to run their trials.

FDA rough estimates of current and future Phase III trials

There are dozens of antibacterial drugs currently in various stages of clinical development. Over the next five years the US Food and Drug Administration (FDA) estimates that approximately 25 antibacterial drugs will complete or enter the late stages of clinical development. The number of drugs will vary over time as some new drugs enter clinical development or some drugs exit development.

Three investigational drugs are currently being evaluated in Phase III clinical trials for hospital-acquired and ventilator-associated bacterial pneumonia (HAP/VAP). Nine more have potential to enter late stages of clinical development for HAP/VAP over the next five years.

Five investigational drugs are currently being evaluated in Phase III clinical trials for complicated urinary tract infections

(cUTI). Three more have potential to enter late stages of clinical development for cUTI over the next five years.

Four investigational drugs either are in or have potential to enter late stages of clinical development for complicated intra-abdominal infections (cIAI) over the next five years.

Five investigational drugs either are in or have potential to enter late stages of clinical development for acute bacterial skin and skin structure infections over the next five years.

There are approximately seven other investigational drugs that have potential to enter late stages of clinical development for other infectious disease indications over the next five years.

Co-ordination problems; why has a network not been established already?

Before governments or civil society partake in a public-private partnership, they should seek to understand exactly what market failures they are trying to address. In this instance the question is thus, why hasn't industry set up its own network if it would mean more efficient clinical trials? As all other clinical trial networks that we are aware of were set up with the involvement of a not-for-profit entity, it seems likely that this may be a necessary requirement for an antibiotic network too. In particular there are likely to be three reasons that could be holding a network back. Until recently there were not enough drugs to sustain a network, industry often isn't good at co-ordinating even when they could both gain and competition law may prove problematic here, and clinical research organisations might not have the capital required to run a network themselves.

Low number of clinical trials until recently

When we examined the number of patients going through clinical trials we found that while there were more than enough patients today between 2005 and 2009 most years did not have enough new drugs to sustain a network. The number of drugs in the pipeline was far lower again between 1995-2005 partly as a failure of the genomic approach to finding new antibiotics⁴. However having

looked at the data for recent years, and the estimates of number of clinical trials that there will be in the future, we believe that there should be enough drugs to sustain a network going forward. This however only explains why a network for antibiotic was not set up before now, and is not in and of itself a reason for a non-profit driven entity needing to enter this space. Having looked at the data for recent years, and the estimates of number of clinical trials that there will be in the future, we believe that there should be enough drugs to sustain a network going forward.

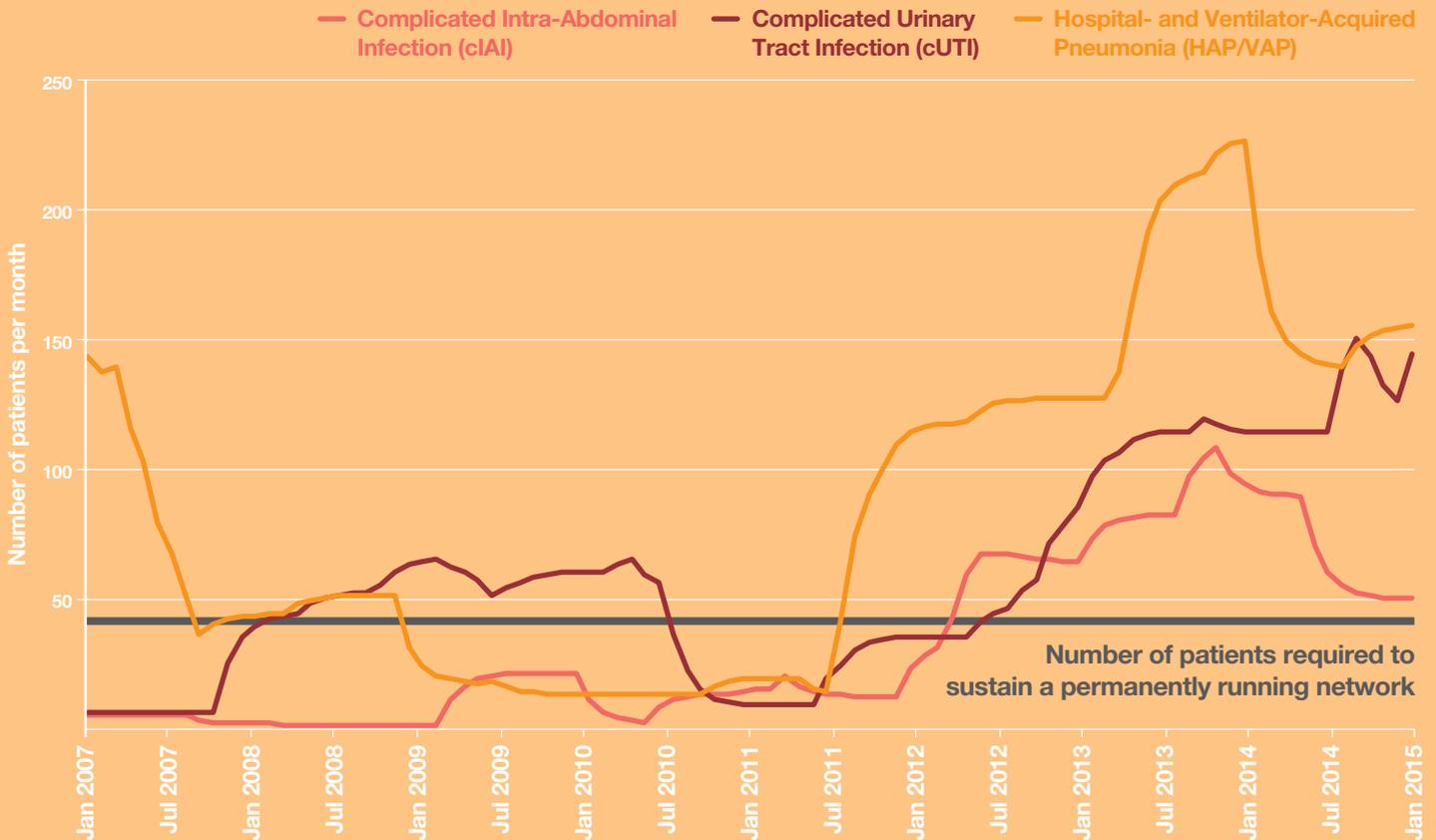
Co-ordination problem and first-mover disadvantage

Often even if it's in two entities mutual benefit to work together, they can have difficulty co-ordinating to do so, because of a lack of trust, or individual incentives that differ from group incentives. In social science this is referred to as a co-ordination problem, the most famous of which is the prisoners' dilemma outlined below.

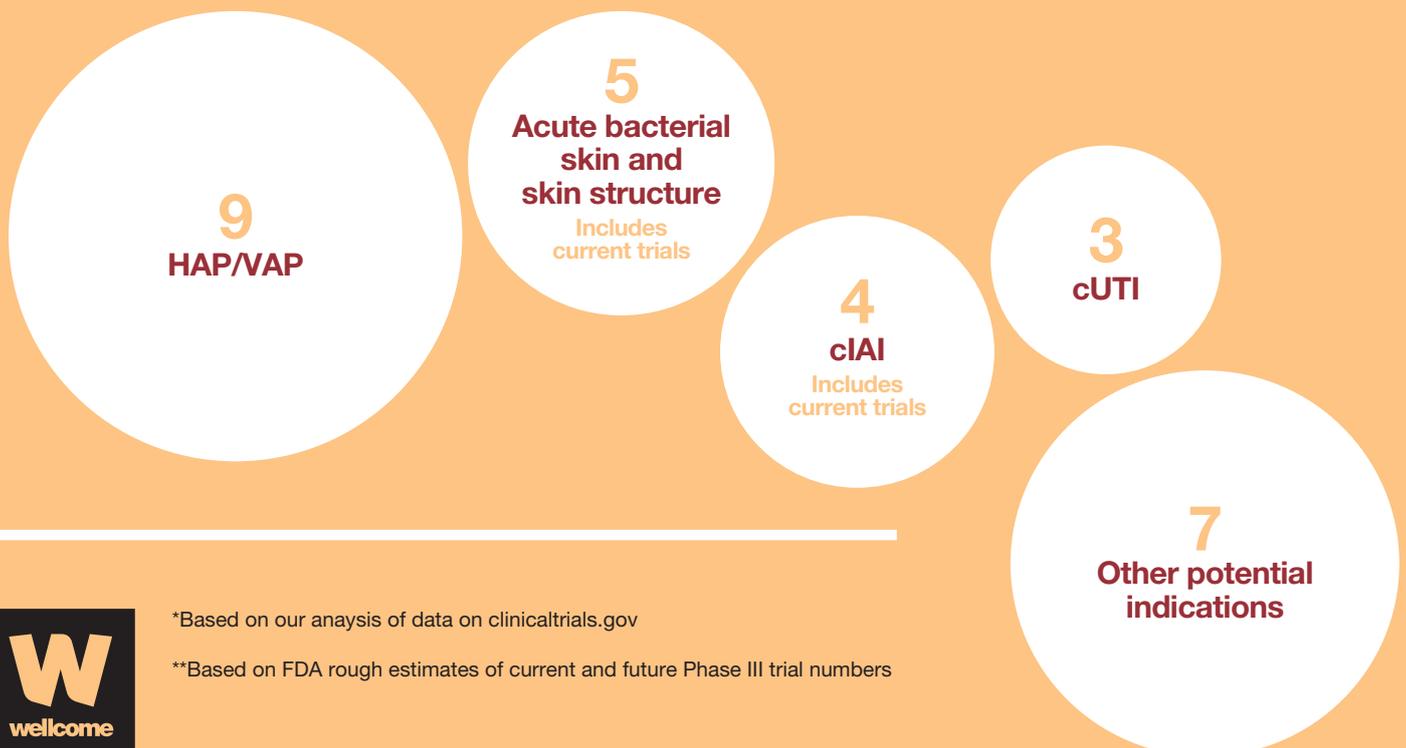
⁴ Livermore, *Discovery research: the challenge of finding new antibiotics*, Journal of Antimicrobial Chemotherapy (2011)

There are enough antibiotic patients to sustain a clinical trial network

Estimated number of network-eligible patients by month*



FDA estimates of new Phase III trials over the next five years**



*Based on our analysis of data on clinicaltrials.gov

**Based on FDA rough estimates of current and future Phase III trial numbers



Example of a co-ordination problem: the prisoner's dilemma

Imagine that you and your partner in crime are arrested. The police suspect you both of committing a major crime, but they only have enough evidence to convict you both for a few months on a minor charge. The police then offer you each a deal, separately: "If you talk and give us evidence on your partner, we will go easy on you." They keep you apart so you cannot communicate, and each of you faces these possibilities:

You now have a dilemma: regardless of whether your partner talks (which you can't know or influence), you will individually be better off if you do talk – and your partner faces the same incentive. But collectively, the best outcome for the pair of you is if you both keep quiet. What you do will depend on how much you trust your partner, how much you think she trusts you, and how much you value the collective good over your own.

Action	Likely outcome	Total prison time
Neither of you talks	3 months in prison each	6 Months
You talk, your partner does not	You avoid prison, your partner does 10 years	10 Years
Your partner talks, you do not	Your partner avoids prison, you do 10 years	10 Years
Both of you talk	8 years in prison each	16 Years

Trust issues similar to the prisoner's dilemma can happen in the market, where firms who are in competition with each other may see a mutual interest in working together but fear that their competitor will somehow get the better of them and thus stay out. For this reason companies are often willing to coordinate in areas with low risk but high benefit, such as setting industry standards for their devices or where strong contracts can be signed to protect themselves, but they are more reluctant to undertake deals that have higher risk, such as agreeing to share infrastructure, where they will become more reliant on each other. Chen et al. have shown that the greater the overlap between two firms' markets, and the bigger the firms, the more tension there's likely to be between them. This tension reduces willingness to take risks together and set up a joint venture and makes those ventures less stable. But this tension is reduced when the firms know that by working together they can achieve something that is not possible alone.

The high hurdle of inter-reliance that is required to set up a clinical trial network could be the reason that none have been set up without public or non-profit involvement. Further to this, the first company to go through a network takes a big risk, as the network

might have start-up problems similar to that of a clinical trial. The gains for moving first could be small, which is why there might be an argument for subsidising the cost of the network for early users. Another factor is that many companies have one drug, which can make this more challenging than the situation where the companies involved have a portfolio of drugs.

Fear of breaching competition law may also be among the reasons companies don't want to come together in this space. Competition law is designed to stop firms working together to reduce the quality of their services or increase their prices to higher than they would be without collaboration. While a trial network set up by industry is unlikely to break the spirit of this law, regulators may fear that a network goes further than just looking at research, or that its aim is really to stop other rivals. An example of this might be larger firms not allowing small firms in a network, to maintain their market dominance. Kevin Outterson from Boston University has stated that pharmaceutical companies might worry about competition rules "significantly delaying a project" and thus reducing its benefit, and that networks will probably be required "to be open access or make some similar concession" before they're approved.

Clinical research organisations lack capital

Often, co-ordination problems are overcome in the private sector by an outside firm that supplies a service to many firms so that they don't have to rely on their rivals. In pharmaceutical research, the obvious companies to do this would be clinical research organisations (CROs) that already work with many different pharmaceutical companies to help them set up their clinical trials.

Like funding a new drug itself, setting up a clinical trial network and selling it privately will rely on the provider outlaying large amounts of capital and time on the network and hoping that it's successful so that it can then recoup its money once the network is up and running. This not only relies on them taking a large amount of risk, but also in them having the capital to risk. The outlays could be hundreds of millions of dollars, and a comparison between the

largest CROs and the largest pharmaceutical companies shows that CROs probably do not have the capital to make this type of investment. Indeed, the market capitalisation of the five largest pharmaceutical companies is more than 40 times that of the five largest CROs. This may explain why CROs are yet to take that risk, particularly as antibiotics account for only a small portion of their revenue, and if the project were successful their mark-up would have to be low enough to entice companies to use the network, meaning potentially limited advantage.

Largest CROs	Market capitalisation⁶	Largest pharmaceutical companies	Market capitalisation⁶
Quintiles (excluding IMS)	\$8.15BN	Johnson & Johnson	\$332.4BN
Covance	\$6.06BN	Novartis	\$200.5BN
Pharmaceutical Product Development	\$3.78BN	Pfizer	\$198.1BN
PAREXEL	\$3.54BN	Merck	\$174.2BN
PRA Health Science	\$3.28BN	Novo Nordisk	\$101.7BN
Total	\$24.8BN	Total	\$1006.9BN

⁶ Based on Yahoo, Google or Bloomberg estimates of market capitalisation as of the 16th of October 2016.

Unique advantages

The GCTS model's main benefits come from connecting hospitals and making it easier to find them and start a trial quickly and efficiently; we've called these "warm base advantages". For the indications in which it can work, a CMP network should be able to find even greater warm base advantages because it uses the same protocol, and on top of this should be able to find efficiencies through sharing control arms.

More work is needed to establish the scale of the benefits that a clinical trial network could generate, and this is one of the areas we've called for greater research on later in the report. For now, we have tried to give rough estimates of the warm base advantages by asking experts what they think the potential savings could be. The figures below are the average of what was suggested to us, and should be seen only as a guide to the potential size of savings that networks could bring.

Warm base advantages

Overview

In order to estimate the capacity of clinical trial networks to make trials more efficient, we combined the Eastern Research Group's (ERG) estimates of different components of a clinical trial. We then estimated how these costs would change with the introduction of clinical trial networks and added the inputs together to estimate the efficiency savings from clinical trial networks⁷.

Source data verification and site monitoring costs

This is the collection of all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of a clinical trial. This is a regulatory requirement and important to ensure that data collected in the trial can be verified as complete, accurate and reliable.

The ERG estimates that this makes up about 14 percent of the costs of running a trial. It was estimated that this cost could be reduced by almost 23 percent, because it is possible to audit multiple trials on the same site and overlapping visits mean that more can be covered on every trip. This would thus lead to an almost 4 percent reduction in the cost of running clinical trials.

Research nurses and clinical research associates costs

Research nurses and clinical research associates are hired specifically for clinical trials. They build multi-disciplinary teams that deliver research, follow up with patients and industry, and collect the data needed to oversee the clinical trial.

The ERG estimates that these researchers account for more than 5 percent of the cost of a clinical trial, which is higher than the costs associated with physicians treating the trial participants. The reason these costs are so high is that at the moment the work that needs to be undertaken by research staff in any one hospital fluctuates depending on whether there is a trial being run in their areas of expertise. This means that they must be hired either on short-term, flexible contracts or as consultants, which tends to be much more expensive than hiring people on a long-term contract. Or, if they are hired in a long-term contract, they have long periods of being underutilised. The estimates we collected suggested that a sustainable clinical trial network to guarantee salary and adequate work would reduce the cost of hiring these staff by 43 percent.

Site recruitment costs

As previously discussed, finding sites for a clinical trial takes time. The ERG estimates that this process costs more than 2 percent of total trial costs. It should be possible to reduce this by an estimated 69 percent in a clinical trial network, as each hospital is likely to run many trials in the network, and so costs associated with enrolling them will be shared between different trials.

The second and potentially more important area where a network can be cost-effective is that trial site recruitment will be expedited, thus accelerating the trial process. This is because it takes a sponsor time to find hospitals who will participate in a trial as well as to recruit efficiently into them. Patient enrolment will also be expedited at the commencement of the trial since investigators will already be familiar with the protocol. McDonnell et al. estimate that it takes between three and six months to find the sites for a Phase II or III clinical trial and that this could be reduced by approximately two months per trial, if there were clinical trial networks in place. This would mean that a drug would be brought to market more quickly, saving roughly the same amount of time in the process that a drug company saves by getting priority review from regulators. Assuming that the company has an 11 percent cost of capital, and using standard inputs for clinical trials (as estimated by ERG and the AMR Review), this would increase the net present value of any sales by 5.5 percent, which means that for every \$1 billion of sales a drug has in its lifetime, this increase in speed would add about \$55 million to its value⁸.

⁷ Eastern Research Group, *Examination of Clinical Trial Costs and Barriers for Drug Development* (2014)

⁸ McDonnell et al, *Efficient delivery of investigational antibacterial agents via sustainable clinical trial networks*, *Clinical Infectious Diseases* (2016) and *AMR Review, Securing New Drugs for Future Generations: The Pipeline of Antibiotics* (2015)

Site overheads and retention costs

Site overheads are fixed costs that are not attributed to any one trial, but instead are pooled between all trials that are operational. They include expenditure such as rent, tools and equipment, computing hardware and software, and management personnel. The ERG estimates that these costs make up 33 percent of the expense in a clinical trial. These costs could be reduced by 32 percent, because there will be a significant reduction of non-productive time lost, it will allow overhead to be utilised all of the time, and it will reduce the pooling cost on individual trials.

Overheads should also be reduced because it will be easier for those running a clinical trial network to ensure that their study sites are efficient. For example, in a one-year trial, if a hospital reports low patient enrolment, it is difficult for researchers to respond to this challenge. By contrast, a trial network that is sustainable for a number of years could simply replace those sites experiencing recruitment problems with other sites.

Site administrative costs

Similarly, we expect the predictability of work and lack of unproductive time to reduce the costs of administrative staff by 21 percent. As administrative staff costs account for about 17 percent of the cost of a clinical trial, this should lead to significant savings.

Data management costs

Data management costs could fall slightly, as a standardised trial means that researchers are constantly testing similar products. The estimates that came in were low, at a 6 percent reduction through clinical trial networks.

Central lab costs

These could be lower because there might be greater efficiencies in putting more data through the same laboratory and labs can plan better as the trial levels will be more constant. As each trial's protocol will be the same, the tests undertaken at the lab will be similar for every drug; this could further lead to efficiencies as the lab could become specialised at doing these tests. Estimates given for this were about 12 percent.

Institutional review board costs

Approvals should be easier and amendments reduced because review boards will be familiar with the protocol design from different trials. However, most people responded that savings here would be negligible or non-existent, so we've assumed that they'll be zero (if a central review board could be established there may be more time and cost savings).

Patient recruitment costs

If a hospital is familiar with the entry criteria and rules of a trial, it should be able to recruit and retain patients more easily, as doctors will have a better sense of patients that should be included. It is established that trials are slow to recruit patients at the beginning, probably because doctors are unfamiliar with the process of doing so. This cost will thus fall when providers commence the trial already knowing the entry criteria well. It was estimated that this cost could fall by 25 percent.

Clinical procedure and patient retention costs

This was not expected to change meaningfully, with an average estimated impact of just 3 percent. This is because the treatment that each patient gets should remain the same.

Physician costs

Similarly, it is not clear if there will be a significant cost reduction here, as patient care will remain the same. It may be easier to train physicians or to follow the protocol of a trial, as physicians are not usually hired for a specific trial. This saving is not likely to be significant: the estimates given average just 4 percent for this.

Total savings

While these estimates are quite rough, we thought it was valuable to have an estimate of the savings from clinical trial networks. If all of these savings are added together, we estimate that there will be a reduction in the cost of running a clinical trial of about 23 percent.

Estimates of potential savings on aspects of clinical trials

Costs	Percentage of total trial cost	Saving estimate
Source data verification and site monitoring	14%	23%
Research nurses and clinical research associates	5%	43%
Site recruitment	2%	69%
Site overheads and retention	33%	32%
Site admin	17%	21%
Data management	0.5%	6%
Central lab	6%	12%
Institutional review board	1%	0%
Patient recruitment	2%	25%
Clinical procedure and patient retention	14%	3%
Physician	5%	4%
Total cost	100%	23%

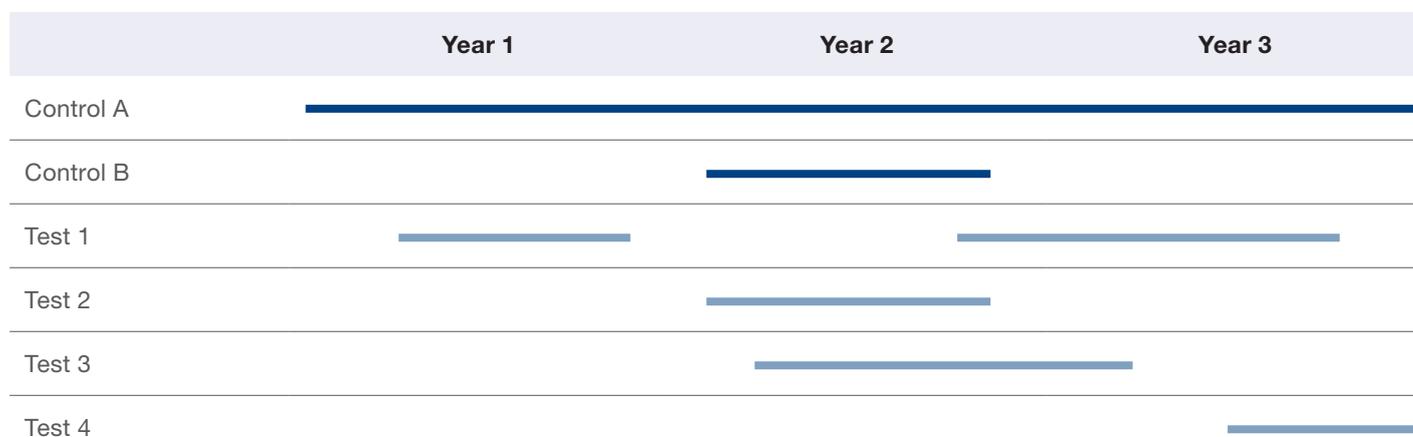
Costs not listed in dollar terms as these vary a lot between Phase II, III and post-approval trials, whilst percentage of cost remains comparable.

Sharing control groups

With a CMP network it should be possible for two or more trials to share a single control group, if there are different studies of the same indication ongoing at the same time. This means that if three trials are each planning to have 500 patients in the control arm and another 500 in the treatment arm, they will be able to reduce their cumulative size from 3000 patients down to 2000. This will reduce the cost as well as expedite the trials.

Illustrated below is a figure showing how the sharing of control arms could work. Rather than establishing a control arm for each new drug, a constant control arm (control A) is envisioned. Multiple agents can be in the network simultaneously, and each compared against the constant control arm. Alternative controls can also be used as needed to address issues such as blinding or substantial differences in how drugs are dosed (control B paired with test 2).

Illustration of how control arms could be shared across clinical trials in a network



This, of course, is only possible if there are at least two trials taking place at the same time. In order to test whether this was the case, we referenced the ClinicalTrials.gov data that we discussed earlier. Here, we reviewed the average number of medium to large clinical trials that occurred each month (defined as a trial that enrolls at least 100 patients).

We found that between 2008 and 2014 there were always at least two medium to large trials running (more than 100 patients) for cUTI

and HAP/VAP that would have met the requirements for a network. Between 2011 and 2014 this was also true of cIAI trials, and while there was always at least one trial running between 2008 and 2010 there were not always two running. On average there were 4.2 trials running every month for each of the three indications. This suggests that there would be sufficient trials running through a network where the control group sharing could meaningfully reduce the size of the control group.

Average number of medium to large trials (100+ patients) running in each month for each indication

	2008	2009	2010	2011	2012	2013	2014	Average
cIAI	1.0	1.8	1.6	2.2	3.7	4.3	3.3	2.5
cUTI	3.8	4.4	3.8	3.0	5.4	9.8	10.5	5.8
HAP/VAP	4.5	2.0	2.0	2.1	3.7	7.3	8.4	4.3
Average	3.1	2.8	2.4	2.4	4.3	7.1	7.4	4.2

In order to estimate the likely savings from sharing control groups, we estimated what would happen if trials all shared a control group the size of the control group for the largest trial currently running in the indication. This found that if a network had been in use between January 2007 and December 2014, the total size of HAP/VAP control groups could have reduced by 68 percent, cUTI by 61 percent and cIAI by 55 percent, with an average overall reduction of 62 percent as highlighted in the adjacent infographic.

Given this, we believe that it is reasonable to estimate that in future the average control group could be reduced by 50 percent, smaller than the reduction estimated for any of the indications. This would mean that on average only 33 percent of patients that were enrolled and randomised in a trial would need to go into the control arm and 67 percent could go into the treatment arm, which would reduce the cost of the trial by a further 25 percent. It would also accelerate the process by a similar margin, as trials would need to recruit fewer patients than they do at the moment.

Control data from earlier periods of network

The final large efficiency that could come from clinical trial networks is sharing of control groups from earlier periods of the trial. By placing patients through a trial with the same entry criteria, protocol and control drug at the same sites, over an extended period, we will hopefully gain a far better understanding of control groups and how consistent they are. This should be useful information in general for those conducting clinical trials. But if control groups in our network prove to be consistent over time, it could also allow

for the borrowing of recent control groups, allowing trials to further reduce the number of new patients they need. And, because this approach makes it much easier to recruit control groups than treatment groups, we can also increase the size of the control group and reduce the size of the treatment group whilst keeping the statistical power of the trial constant.

As an example, consider a trial that would previously have enrolled 350 patients in each arm. Instead, it could now enrol 425 control-treated patients (100 randomised in parallel, 325 from prior work) alongside just 300 treatment patients. 425 in one arm and 300 in another has the same statistical power as 350 test-treated patients paired with 350 control-treated patients. In effect, a mature network could utilise this strategy to generate data equivalent to that of a stand-alone 700-patient trial whilst only needing to enrol 400 new patients, thus yielding a total time and cost reduction of 43 percent for that and future trials using the same comparator and protocol⁹.

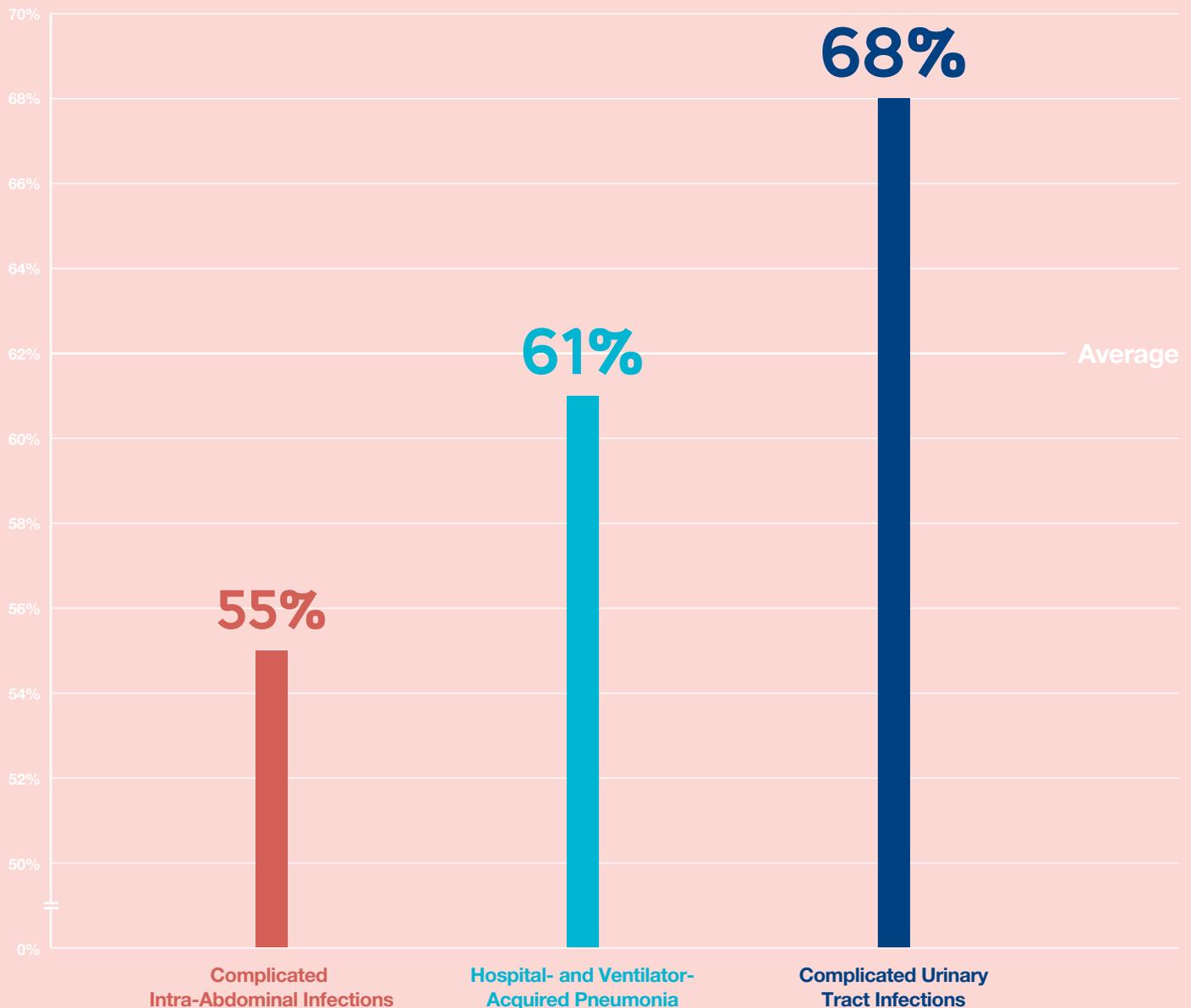
To bring in control groups from previous periods we need to find a way to track and take account of changing standards of care for the control group (these are likely to be incremental), and to track whether resistance levels have changed and the epidemiology of the pathogens are similar. How to monitor these changes, and at what point difference between past and present control groups become too great to use the data in current clinical trials, must be answered satisfactorily before this method is used, and we are unlikely to know whether this type of control sharing is possible until the network is up and running. For more on this, see the 'Next steps and research needs' section.

⁹ Having either the treatment or control group be larger is common in some types of clinical trials when one intervention costs significantly more than the other. However, this is rarely the case in medical trials. See Esther Dufo's *Using Randomization In Development Economics Research: A Toolkit* (2007) for more.

Sharing control groups would have reduced their required size by 62%

This was estimated by assuming that all trials running for a given indication would share a control group the size of the largest currently in use

Control group saving by indication



We included all phase II, III and post-approval trials in the given indications, that could have been tested in a contentious master protocol trial. This means that they were in adults with infections susceptible to first line treatments for the three given indications.

Potential total financial savings

The following is an example of how the efficiencies created by clinical trial networks, coupled with sharing of control arms and use of previous control arms, could affect two organisations, each running a 700-patient trial simultaneously. At the moment, they have to spend time vetting and enrolling hospitals. Instead, each could now tap into a network and quickly identify hospitals that they know will be efficient. This could reduce their costs by 23 percent. They could then share one control arm between them, instead of each funding their own control arms; this would reduce the combined number of patients needed by 25 percent. Finally, if the network is well-established and functions as consistently as anticipated, the sponsors should be able to draw on previous work for some of their control patients, reducing the need to fill both control and treatment groups. So, where the two trials would previously have needed 1400 patients between them, they would now only need 700 (100 joint control, 300 in each treatment arm, with another 325 control patients coming from previous trials) to maintain the same statistical power. This reduction, coupled with the efficiency savings, could cut the cost of a clinical trial by more than 60 percent and accelerate the trial process significantly.

While the exact nature and efficiency of a clinical trial network will not become accurately known until one is established, and many reading this may be understandably sceptical of the size of the savings that might be made, it is nonetheless clear to us that if a network is well executed the potential for improving clinical trials – and, by implication, facilitating the faster discovery of new drugs – is vast. The adjacent infographic highlights the impact that different savings could have on the financial lifecycle of a drug.

Other advantages

Predictability

For many uncertainties over the scale, duration and ‘acceptable’ endpoint for Phase III registration studies are an issue. This is especially true for companies with a single antibiotic asset. Established clinical trial networks will not just reduce the costs but make them much more predictable. A single master protocol in combination with the time benefits seen with ‘warm base’ sites and the cost savings highlighted earlier in this document will reduce the total cost and time to complete late stage studies. For all this improves the market dynamic and NPV. For smaller companies, with perhaps a single asset, seeking exit this is particularly welcome as better defined costs and the potential for a nearer term exit, which

the improved timelines bring, markedly reduce financial risks for companies and enhance value earlier in the development cycle.

Other studies

Staff at University College Hospital in London have said that they found that when hospitals became research hospitals, a culture of running trials and undertaking research becomes embedded. It is hoped that by creating sites that constantly run trials of antibacterials, as both of the models we have discussed have the potential to do, a similar research culture will be established within these hospitals’ infectious disease units. This, combined with the fact that much of the infrastructure to run studies will already be in place, should make it possible to run parallel studies without too much difficulty. This could reduce the cost of studying diagnostics and other tools greatly.

Further to this, the demand for the clinical trial network will vary over time. During times when the infrastructure is underutilised, running non-time-critical optimisation studies could be very cost-effective. These studies could range from dosing to increasing patient supervision, and the long trend of data showing how control groups fare in different hospitals should also make it much easier to run hospital-level randomisation, as might be required by some types of interventions, such as studying the impact of increasing nursing staff.

Training opportunities

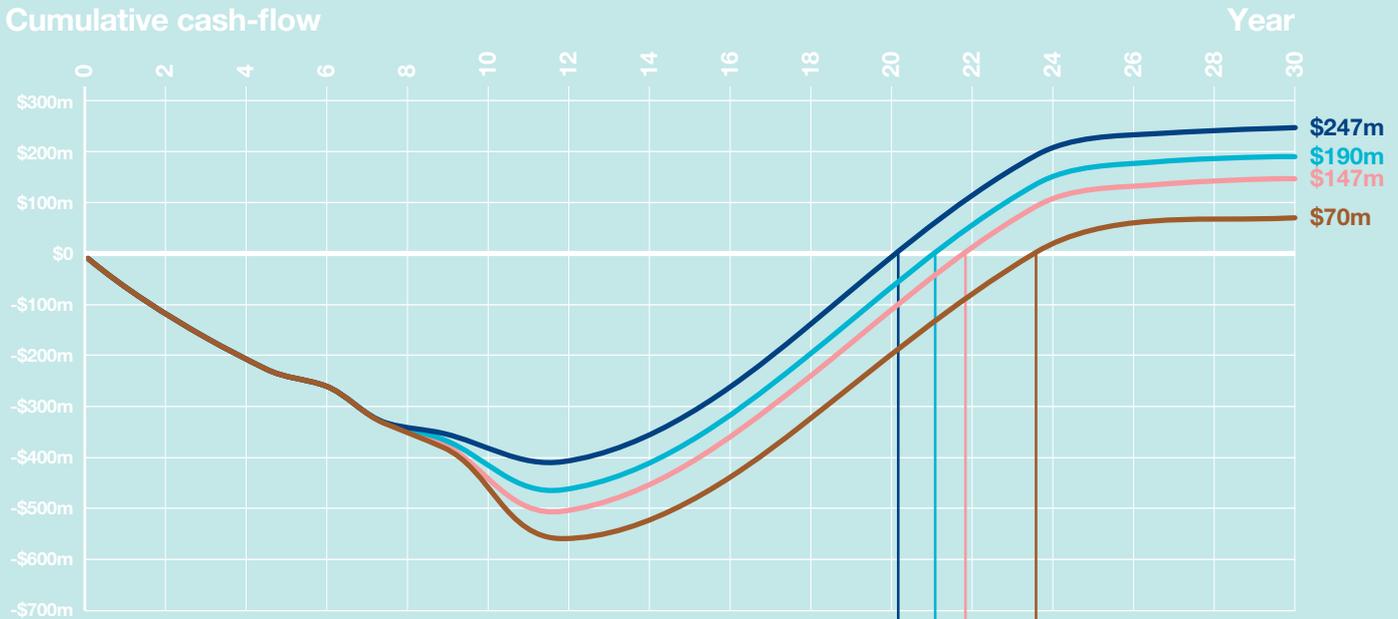
We hope that the existence of a network would both provide multiple training opportunities and create a community of skilled investigators. As the network would be “turning the crank” very regularly, new (or visiting) staff could predictably experience the process of trial implementation. In a period of as little as a month, a visiting scholar would doubtless see the entire process in action (and perhaps across both a main trial and a secondary trial). Viewed from the other direction, the stable community of investigators would be a resource for placing parallel trials as well as a network of experts on trial implementation.

Understanding of control groups

Under the CMP model, there will be control groups continuously running in the same hospitals over an extended period. This should improve our understanding of control groups and how they work,

Clinical trial networks will improve the profitability of antibiotics

Financial life cycle of a typical antibiotic



Break even points

C. Scenario B with additional savings from previous control group data

20y 2m

B. Scenario A with additional savings from trial sharing from a Continuous Master Protocols

21y 1m

A. Savings from Globally Connected Trial Sites

21y 10m

Baseline, as estimated by the Review on AMR

23y 6m



The above data was based on analysis published by the Review on Antimicrobial Resistance in the report "Securing New Drugs for Future Generations – the Pipeline of Antibiotics" (2015). In that report the Review showed how an average antibiotic developer spends about 14 years investing money in an antibiotic, before they start to get a return on their investment. At about year 23, a drug breaks even and then at about year 24 after the start of their research, the patent expires and sales revenue level off as the price goes down. Scenario A reflects savings against the base case scenario

resulting from a Globally Connected Trial Site Network (this allows a shortening of set up time by a combined 4 months and reduces the cost of Phase II, III and Post Approval trials by 23%). Scenario B builds on scenario A, with a further reduction in trial costs of 25% due to the smaller control trials that would be needed with a Continuous Master Protocol. Scenario C builds on B, with a further reduction in trial costs by 25% owing to the savings that would be possible if clinical trials could use control data from previous trials to replace some contemporary data.

letting us better understand phenomena like random lows (where by chance a group of poorly performing patients are recruited to one arm of the trial) and how prevalent they really are. Tracking control groups over time may also help us learn more about the things that impact on patients' survival chances.

Regulatory approval

If most drugs are tested with the same protocol, in similar hospitals, against the same control drug, regulators are likely to become very familiar with this system. This will make it easier for them to judge the efficacy and safety of a drug. Better understanding of control groups should make this easier, too.

A second advantage for regulators is that clinical trial networks should reduce instances of bio-creep. When effective, antibiotics are both quick and curative. And, since it is not ethical to use a control drug that will not work, this means that it is very difficult for a new antibiotic to show that it is superior to previous generations. For this reason, regulatory agencies have taken to accepting non-inferiority trials as proof that an antibiotic is adequate. This means that new antibiotics have to show that they are not worse than gold standard antibiotics by a clinically important margin. The worry with this approach is that the trial drug might genuinely be slightly less effective. Whilst this is a problem, the trial process is rigorous enough to make sure that any gap between the two will be small. However, in time, that trial drug might become a standard treatment and the control arm of clinical trials. Then, again, if a non-inferiority trial is used, another slightly inferior drug might get approved, and could then become the control drug in a future clinical trial. While each iteration of this process is deemed acceptable, the risk is that without realising it, there is a steady deterioration in the quality of the drugs, or bio-creep. By standardising the process by which drugs are trialled, by ongoing review of the performance of available therapies, and by use of a standard high-quality comparator¹⁰, bio-creep will become far less of a concern, thus making non-inferiority trials more reliable.

While a clinical trial network could be advantageous for regulators, it is important to ensure that the system is set up in a way that works for them, too. If pharmaceutical companies are not confident that a network will provide as good a path to regulatory approval as running individual trials, then they will not participate.

¹⁰ Davis and Fleming, *A simulation study evaluating bio-creep risk in serial non-inferiority clinical trials for preservation of effect* (2015)

Practicalities

Data management

General release

We believe that in the fullness of time, high-level data and anonymised patient-level data on a clinical trial should be released to those with a legitimate interest in examining them, as is becoming the norm for all medical trials (such as clinicalstudydatarequest.com). Questions of how and where to release this information are important, but not unique to clinical trial networks. In order to reduce costs and increase ease of access, the network should link up with an already established clinical trial depository such as Clinical Study Data Request or Yale Open Data Access. These sites both have independent review panels to adjudicate whether a researcher should be able to access anonymised patient data, in order to ensure patient privacy whilst giving researchers the important access they need.

There are, however, some issues that are unique to clinical trial networks. If two drugs are studied in the same clinical trial protocol, in the same hospitals, with the same control drug, it will likely become possible to make statistically valid comparisons of two different drugs that were not trialled against each other. While this might make it easier for physicians and regulators to assess the relative merits of different drugs, which would in turn benefit patients and healthcare, without adequate consideration of whether the trial is powered for this comparison it is not clear how much information could be gleaned from these comparisons. This issue was discussed at the conference we held in October 2016, and it was pointed out that this type of comparison already happens, but across datasets generated using different designs and objectives, so there would be some advantage in making it more accurate. Although it might be argued that only those with inferior drugs would lose out from such a comparison and that those with better products would gain, the larger concern is that comparisons might be underpowered. Further, the well-known problem of multiple comparisons would quickly emerge: if enough comparisons are done, seemingly significant differences will begin to be seen by chance. This issue would require careful advance planning: of those polled in the audience, 51 percent said they thought this would be useful, whilst 8 percent thought it not useful and 11 percent said it would stop them using a network; the other 30 percent were unsure.

Secondly timing of data release could be a factor if some drugs have completed, but the broader trial and associated control arm is still ongoing. Data are not usually released until trial completion. This would be a break with how trials are normally undertaken, while we can foresee any specific issues with this, that does not mean they do not exit.

Information for sponsoring organisation

The company conducting the trial should get the same information that they get at the moment from sites. However, there may be more than one trial ongoing at any specific time; if this is the case, only the control data and the treatment data for their specific trial should be shared with a sponsor. This data will be commercially sensitive and very valuable to the sponsor, so it is important that they are assured that only they will initially have access to their data. It is also very important for the patients involved to know that their data are secure and will not leak. In areas such as tax receipts, accounting and banking, highly valuable information is stored in a secure fashion, and is also often partially shared with government authorities, their clients, etc. It thus should be possible to create a similar system for clinical trial networks.

Consent and institutional review boards

We believe that it would be too imposing to establish and require a single Institutional Review Board (IRB) of Record for the network under the current regulatory framework. At the moment, each country or region has its own regulatory IRB framework, with some countries allowing a Lead Ethics Committee to be the umbrella system. When obtaining IRB or Ethics Committee approval, the network should aim to utilise the most streamlined system available to that country, and aim to design its protocols in such a way that it meets the criteria for all the areas involved in the trial. However, a network may be well placed to tap into an IRB platform in the same or different countries, making this process easier, and any work that can be done to harmonise the IRB process would make a global network and global research easier.

Managing entry and exit of investigational drugs

As all of the agents being taken on by a network will be in Phase II, Phase III or Post-Approval trials, drugs will be able to be identified 12-24 months prior to the start of these phases based on first subject in Phase I trials. We recommend that any network maintain a database of Phase I trials and use this to contact sponsors about their plans for specific indications. If the network is successful, we would expect that in time, sponsors will pro-actively contact the network regarding their aims.

While attrition will make it impossible to predict exactly how many drugs will make it into Phase II and Phase III, a standard attrition-based approach to estimating likelihood of progression

to these phases should allow the network to estimate how many trials are likely to take place in later phases, and hopefully adjust its capacity to meet this demand.

Capacity limits would be addressed as they arise and issues should be visible long in advance. Reaching a capacity limit is a positive finding for the global pipeline, and will show that the network, as initially planned, has been successful. One way to view this is that compounds can probably always be added – but the introduction of additional compounds will slow the progression of all compounds. Some of this slowing may simply be making visible the kinds of delays that occur when trials compete with each other for sites as already happens. Capacity modelling should be undertaken to ensure that the network has capacity for the most likely average compound throughput rate. Based on our modelling, this would seem to require capacity for 2500-5000 patients a year between HAP/VAP, cUTI and cIAI.

Blinding within a continuous master protocol

Blinding patients when there is more than one drug being trialled could be difficult as different treatments will require doses at different times, and some might be oral whilst others are intravenous. There are three different approaches that could be taken here, and more work will need to be done with regulators and study co-ordinators to work out which is best.

Randomisation by cohort

Randomisation by cohort would mean that in every hospital patients are openly randomised onto one of the trials currently being run. Following this there would be a double-blind randomisation onto either the control or treatment group. Each drug would use control patient data from every cohort but only treatment data from its own. The downside of this approach is that control patients from different cohorts will be on different dosing schedules. Physicians will also know which patients are in which cohort, which could influence their behaviour; however, as they still won't know if the patient is in the control or treatment group, this shouldn't be a problem. There may also be challenges regarding the pooling of such information, and demonstrating that the efficacy and safety profile are similar across regimens. However, a similar response should be expected if both possibilities are approved regimens, and may simply require a review of the data for consistency. It may also be possible to hide which cohort is testing which drug, so that doctors know which patients are in cohort A and which are in cohort B, but not

which cohort is testing which drugs, nor which patients are in the treatment group and which are in the control. This might not be possible and will depend on the similarities between the drugs and on the doctors' knowledge of the trial.

Double-blind, part-placebo schedule

Under this system a control drug would be given at midnight, 8am, midday and 4pm, with the drug infused over two hours. The treatment drug could then be dosed at either 8, 12 or 24 hours depending on its requirement. There would need to be two protocols, or at least cohorts, within this system to distinguish between trials on oral and intravenous drugs. The problem with this system is that it pushes doctors to give patients many treatments they don't need, which could be time-consuming or possibly have a negative effect on the patients' recovery.

A variant of this approach may be possible in which test agents are always added with a control arm of minimal complexity. This test-control dyad could be identified because of its dosing pattern, but it would still not be apparent to an observer whether the patient was on test or control.

Open-label studies

Finally, open-label studies could be used to compare the difference between the two groups. If the end points the clinicians are measuring are not open to interpretation, such as measuring mortality rates, and both drugs are expected to work, then open-label studies should provide the same standard of data as double-blind studies. This approach was taken by Tracking Resistance to Artemisinin Collaboration, a malaria network. Work with regulators would need to take place in order to establish if this would be acceptable for antibiotics.

Next steps and research needs

There are many questions that we think should be answered in more depth before a clinical trial network can be established. We have drawn up a list of the areas we believe should be researched in more depth in order to help create a clinical trial network. All of this work should be achievable within a year and would offer good value for money for anyone seriously considering funding or establishing a clinical trial network for antibiotics.

Learn lessons from previous networks

A large number of clinical trial networks already exist. The most prominent network in the antibacterial space is run by the Antibacterial Resistance Leadership Group (ARLG), which is funded by the US National Institute of Allergy and Infectious Diseases. The ARLG “develops, designs, implements, and manages a clinical research agenda to increase knowledge of antibacterial resistance”. It implements its work via a network of networks, often running open-label or observational studies that help track resistance and help optimise the treatments we have against drug-resistant infections. It’s also important to co-ordinate with organisations like the ARLG and COMBACTE, a European research network, in order to reduce unnecessary duplication.

In areas such as malaria, TB and HIV, large networks have been used to help reduce costs, find patients in remote areas, track resistance and run large trials quickly, such as the Tracking Resistance to Artemisinin Collaboration and Europe’s Prepare network.

In cancer, several networks exist that have made it easier to find rare patients. Examples here include the I-SPY and Lung-MAP networks.

An effort should be made to reach out and speak to all of the clinical trial networks that exist as well as those who work with them, to assess their strengths and learn lessons from their work. It would be useful for medicine as a whole to track the success of networks in different areas and could be invaluable for those seeking to set up a network for drug-resistant infections.

Assess user interest and requirements

As well as learning from other networks, more work needs to be undertaken to reach out to those who are likely to use a network. We need a better sense of how people who could use the network think it should be designed and funded. We have already done

a lot of this work, particularly when we held a conference at the Wellcome Trust. While most of the people who attended were in favour of setting up a network, views differed greatly about what a network should look like. Further views should be sought in a systematic way, to decide how to set a network up.

Secondly, this process should model the likely uptake of a network for different indications. We have shown that there are enough trials done on HAP/VAP, cUTI and possibly cIAI infections to sustain a network focused on each such infection. But future work needs to build on this by looking at what proportion of those trials will actually enrol in a network, assessing other indications, and coming up with more robust ways of estimating future use of the network.

An assessment of user interest should not only look at the pharmaceutical industry, but should also assess the needs and desires of academia, government, diagnostic companies and anyone else likely to use a network. It is important that a network focuses on the needs of all stakeholders, so as to maximise its benefits.

Can we accelerate registration via continuous disease-specific master protocols focused on UDR pathogens?

A continuous disease-specific master protocol offers great potential to both accelerate and reduce costs of initial drug registration. As initial registration in at least one indication is the key gateway to broader investigation of a new agent’s utility, efficient delivery of those investigations has obvious value. As recent experience have made it clear that new agent registration can only proceed reliably when focused on a standard infection in the setting of UDR pathogens, it is clear that many such trials will be run. In that event, there is great value in ensuring this is done efficiently. Our initial estimate suggests that savings could be 40 percent in terms of both time and cost for any given Phase II or Phase III investigation of a new agent, and even greater if the use of previous control trials is possible.

There are two parts to this. First, it needs to be established in what indications it would be useful to have a master protocol. This can be done in part when assessing potential user interest and modelling uptake, along with examining the logistical challenges and potential benefits for areas with much lower trial rates (such as paediatric care and narrow-spectrum drugs) and assessing whether a master protocol would be useful for community-acquired infections (such as gonorrhoea).

Following on from this, a draft master protocol should be drawn up for at least one indication. The general opinion at the conference was that cUTI and HAP/VAP were the most useful indications to test. A protocol should be drawn up to the standard that all drugs meet before trial. This should involve working with a CRO, regulators, academia and industry in order to establish a protocol that would allow different drugs for an indication to be included in it. Critical issues to resolve will be blinding, dose adjustments, drug-specific inclusions, the approach to safety reporting, database integrity, and database sharing. Discussions at the recent workshop suggested each of these problems might have solutions, but this needs to be confirmed by working through the details of a specific protocol or two.

Statistical issues for continuous master protocols

The pooling of control arm data across time periods is generally reasonable under a single master protocol over a “reasonable” time frame, provided ongoing review of data from different time periods suggests this is acceptable. However, if the trials in the network are conducted using different protocols, pooling may be more challenging due to differences between protocols and study conduct. This would therefore require a closer evaluation of the similarities in design of the trial protocols (and the observed data), particularly in relation to the time period, geography, sites and epidemiology of pathogens.

Type I error (false positive) control questions are often raised when statistical analyses are performed on a number of comparisons. In this case, there is a view that any type I error should be controlled at the drug level rather than at the trial level, meaning there is little need for multiplicity adjustment. Further evaluation and discussion with the FDA and the European Medicines Agency (EMA) is necessary in relation to the platform trial having a control arm response on a random low (which could inflate type I error for all drug comparisons).

Possible actions are: (1) discussion with EMA and FDA regarding the likelihood of a random low affecting type I error when the control arm data are drawn from a broad study population usually seen across multiple studies, and over a longer time period; and (2) possible simulation work – in its simplest form this could take the form of simulating 1x5-arm trials versus 5x2-arm trials.

Changing the randomisation ratio seemed reasonable and during our discussions no particular statistical issues were raised. However, it is necessary to consider a minimal amount of information from each time period to allow a reliable view on

similarity of control arms across time periods to justify pooling. This would need to be explored for a real case when the master protocol is being developed.

Site overview

As a priority, an overview is needed of the number, type and size of sites to be included in a clinical trial network. At the moment a significant number of sites do not enrol any patients, and the number of patients a site enrolls tends to increase over time. As previously discussed it is expected that a clinical trial network will be able either to improve or remove sites that are not enrolling enough patients, but to what extent this is possible needs to be assessed. This will feed into work examining the benefits of clinical trial networks as well as gauging what is needed for implementation.

Further to this, work should assess questions like the locations sites should be in, looking at the advantages and disadvantages to using sites from a large number of countries or focusing on a few. Regional distribution is also important; it is hoped that a network would be truly global but the feasibility of this should be studied. It should examine the difficulties with running trials in income-constrained environments, such as the weaker standard of care, and see how these sites could be included. Different countries have different standards of care, and depending on drug resistance in their areas are likely to use different drugs to treat UDR infections. We thus need to assess what issues this creates for running a network.

Finally, people in industry want to see a network that investigates novel therapies for drug-resistant infections. The above-discussed CMP may only function efficiently if focused on UDR infections where a reliable global comparator is possible. On the other hand, studies of highly resistant pathogens will either be open-label or be randomised vs best available therapy, defined on a case-by-case basis. Is it possible to find sites able to run these trials in areas of high resistance and include these in a network? Work needs to be undertaken to see if we can find hospitals where multiple-drug-resistant infections are very common and that are also suitable to run a trial.

Other advantages of a network

This paper has sought to highlight the benefits a clinical trial network can have, in terms of speeding up clinical trial networks,

sharing trial expertise and reducing the costs. However, we've been limited by time and resources. More work thus needs to be undertaken on modelling the use of a network, the benefits to sites and lab services, the reduction in trial time, and the benefits for training, diagnostics and other areas. As much as possible, this work should identify the various beneficiaries and quantify the benefits monetarily.

Governance

The potential governance structures for a network should be examined, by exploring the structures of other networks and similar organisations. Working with stakeholders it should then be determined which processes are likely to work best.

Funding and establishment

An inventory should be drawn up covering what needs to exist for a network to function, how many hospitals should be included, what the lab requirements are, and what the staffing needs are.

In this paper we have tried to examine the costs and benefits of a network at a high level. It is hoped that going forward this work will be built on by a more detailed analysis of the costs and benefits of setting up a network as we've outlined. The estimates of advantages from a network need to be combined with expected uptake in order to estimate start-up costs and how much of these need to be funded by the public sector. Use and costs should be modelled over the programme's first 10 years with optimistic, pessimistic and standard assumptions, in order to best estimate costs and show what long-term exposure (if any) funders might face.

Following on from this now, work should start to examine different funding approaches and see what industry, government organisations and others are willing to pay in order to set up a clinical trial network. This should include looking for companies who would be interested in placing their drugs into the network at its beginning, as well as those who might be willing to pay money to establish the network in return for lower fees later on, a seat on the organisation's board or some type of preferential treatment. Finally, this piece of work should map out a process for recruiting sites as well as drugs and get them up and running, so that if clinical trial networks get funding, there is a blueprint available to start the process.

Conclusion and overview of working group

This document aims to highlight the challenges and benefits of creating a clinical trial network. While there are many questions to be answered about the best way and practicalities of creating a network, we believe that such a network has tremendous promise to reduce the cost and time taken to run clinical trials and to improve the standard of data and access to patients, making it easier for new antibiotics to be created.

Anthony McDonnell

Head of Economic Research for the AMR (O'Neill) Review

Marco Cavaleri

Head of Office for Anti-infectives and Vaccines,
European Medicines Agency

Ed Cox

Director for the Office of Antimicrobial Products for the
US Food and Drug Administration

Aaron Dane

Statistical Consultant and Director of Dane Stat Consulting

Herman Goossens

Director of the Department of Clinical Pathology at the
University Hospital of Antwerp

Ian Hayter

Projects Director at Destiny Pharma

Chris Houchens

Branch Chief for the Antibacterials Program at the
Biomedical Advanced Research and Development Authority

Tim Jinks

Development Lead for Drug Resistant Infections at the
Wellcome Trust

This document was written by a working group led by Anthony McDonnell and funded by the Wellcome Trust. All working group members are listed below. All of them have taken part in the working group in a personal capacity; any views expressed by the working group should not be attributed to any one individual or their employer.

Joe Larsen

Deputy Director (acting) of the Biomedical Advanced
Research and Development Authority

Stephen Mikita

Attorney and Special Patient Representative for the
Food and Drug Administration

Gareth Morgan

Senior Vice President for Portfolio Management at Shionogi

John Rex

Senior Vice President and Chief Strategy Officer,
AstraZeneca Antibiotics Business Unit

Konji Sebati

Chief Executive Officer for the Innovative Pharmaceutical
Association of South Africa

Pamela Tenaerts

Executive Director at Duke University, Clinical Trials
Transformation Initiative

Andrew Thomson

Statistician, Office of Biostatistics and Methodology Support,
European Medical Agency

Keiko Tone

Vice President for Market Access at Shionogi

Acknowledgements

We would like to thank the Wellcome Trust for funding this project and hosting a conference on clinical trial networks, as well as providing logistical and analytical support for the working group. We also thank the Review on AMR for starting this project, and its continuous input into the process, as well as all of our employers for allowing us the time work on this and in many cases providing additional resources to help us undertake this research. We are grateful to The Block Studio for designing our infographics and typesetting this paper. Finally we'd like to thank everyone who came to our conference in London, less than 20 percent of attendees were based in the UK and half were from outside of Europe. It was humbling to see so many experts in this area give their time to comment on our work, and give their views on clinical trial networks.

Wellcome exists to improve health for everyone by helping great ideas to thrive. We're a global charitable foundation, both politically and financially independent. We support scientists and researchers, take on big problems, fuel imaginations and spark debate.

Wellcome Trust, 215 Euston Road, London NW1 2BE, UK
T +44 (0)20 7611 8888, F +44 (0)20 7611 8545, E contact@wellcome.ac.uk,
wellcome.ac.uk

The Wellcome Trust is a charity registered in England and Wales, no. 210183.
Its sole trustee is The Wellcome Trust Limited, a company registered in England and Wales, no. 2711000
(whose registered office is at 215 Euston Road, London NW1 2BE, UK). PE-6512/08-2016/MC