www.christopherssmile.org.uk

"Our vision is for every child diagnosed with childhood cancer to not only survive, but to reach adulthood enjoying a good quality of life."

Improving the availability of innovative treatments for children with cancer

“we're still treating cancer with mediaeval treatments”

Professor Alan Ashworth - Chief Executive The Institute of Cancer Research
BBC Horizon 2010

Contents

1 Introduction

"Cancer is a disease that only affects older people."
If we had been told this on the 22nd October 2006 we would have been in agreement. If the same thing had been said to us on the 23rd October, a day later, we would have been in violent disagreement. The difference being on the 23rd October 2006 our 4 year old son Christopher was diagnosed with a brain tumour. Two days later we were informed that the tumour was metastatic Medulloblastoma and that Christopher would be extremely lucky to survive. As it transpired despite his determined battle for 21 months there were no treatments that could save him and he lost his fight on the 5th June 2008, nine days before his sixth birthday.

Sadly Christopher was not an isolated case and during our time in and out of hospitals we encountered many children with cancer who like Christopher are no longer with us. The treatments available to Christopher and his peers were essentially the same as those given to children with cancer for decades – surgery, cytotoxic chemotherapy and radiotherapy. These were the treatments that Professor Alan Ashworth described as 'mediaeval' in the [(1)] 2010 BBC Horizon television documentary. None of the chemotherapy drugs provided to Christopher were approved for use on children and were used 'off label'. Surgery and radiotherapy can leave a child impaired for life. Our choice as parents was either watch our son die or treat him with drugs that had an average age of nearly 50 years and side effects that would have impaired him for life. These are the choices no parent should have to make.

In October 2008 we set up Christopher's Smile to make a difference in bringing new treatments and new hope to the 25% of children with cancer who do not survive their disease and also the survivors who battle daily with the legacy their treatments have left them. We have learnt a lot since October 2008, many negatives and very few positives. We have met politicians, academic researchers and members of the pharmaceutical industry, none of whom give us the confidence that the issues documented on the following pages will be addressed as a matter of urgency.

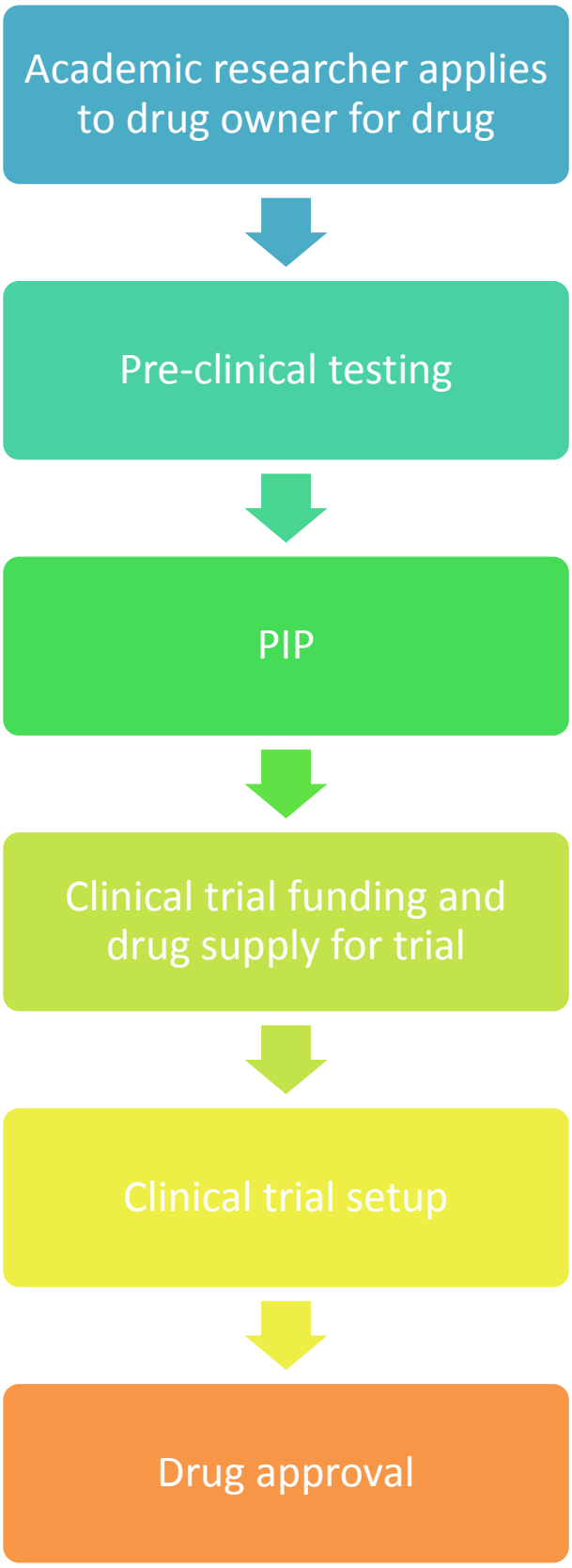
There have been huge advances in the understanding of cancer genetics since we lost Christopher in 2008. These discoveries have been helped by the new technologies that are becoming available at an ever increasing pace. Plans are already underway for the introduction of personalised cancer treatments for adults using combinations of innovative novel agents. These drugs have none of the devastating side effects of chemotherapy. These novel agents are not available as front line treatments for children.

In the following pages we document the issues with paediatric oncology drug availability and we present propositions for change which would result in improvements for children with cancer.

Without change the outlook for children with cancer is bleak.

Karen and Kevin Capel 2013

2 Obstacles within current process for identifying, trialling and approving drugs



Academic researcher applies to pharma for the supply drug for pre-clinical testing. In some cases pharma companies will approach academic researchers with a new drug for pre-clinical testing. In all cases novel drugs are supplied with conditions set by an MTA

Dependent on charity or MRC funding and the availability of cell/tumour models as well as novel agents

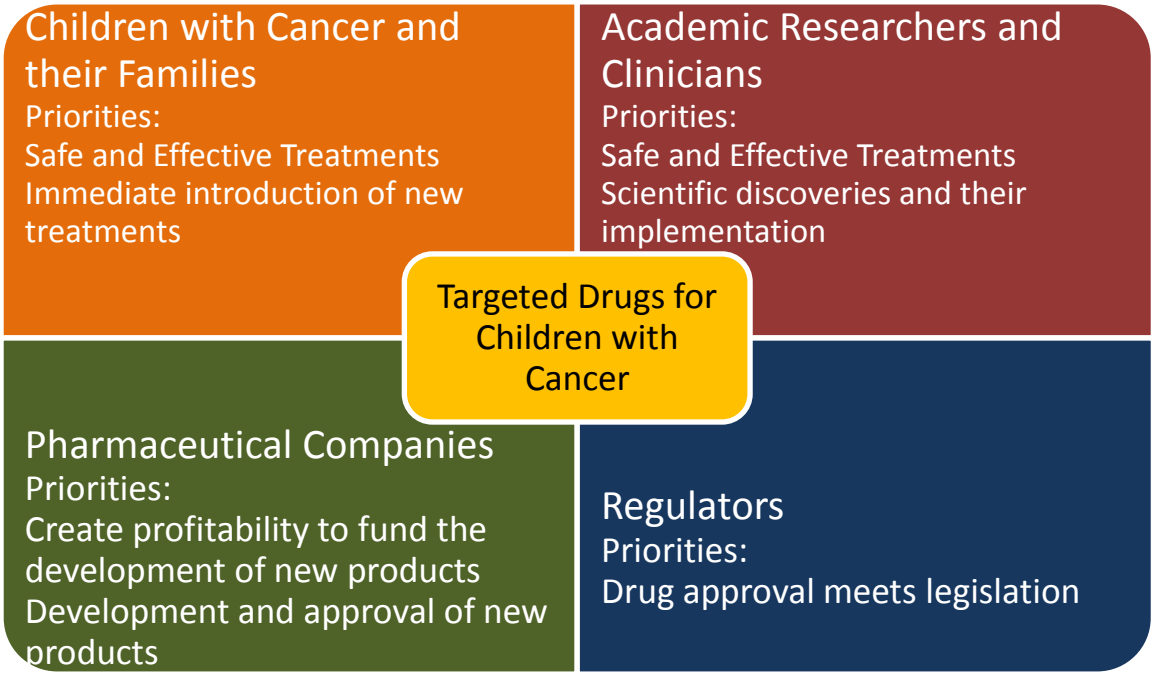
PIP process allows pharma to apply for waiver based on disease type and not mechanism of action. PIP process needs too much detail of clinical trial content prior to implementation

In the UK only sources of trial funding is CRUK or pharma. Agreement from pharma needed to supply drugs for trial. No obvious process for supply of drugs if trial requires novel products from 2 or more pharma companies.

There is one process regardless of size of trial and no fast track process. Trial methodologies must evolve to remove randomisation and include targeted biological selection of candidate patients.

Following 3 phases of clinical trial and subsequent results publication drug can be considered for approval by the regulatory authority

The 4 main groups involved with the introduction of innovative treatments for paediatric malignancies are the following:



Each group has their own priorities and there is no single focus on providing children with safe and effective treatments for cancer. There is no single strategy to bring about change and only a loose working arrangement between Academic Researchers and Clinicians, Pharmaceutical Companies and Regulators.

3 Background and Issues

3.1 Material Transfer Agreements

3.1.1 Background

A Material Transfer Agreement (MTA) is a contract that governs the transfer/exchange of tangible research material (namely, between two organisations), and often where the recipient intends to use the material for their own research. The MTA is used to agree the:

- permitted use of materials
- prohibited use of materials
- access to results
- confidentiality
- publications
- use of results
- ownership of resulting IP
- royalties from any activities generated by the recipient

In the case of agents supplied to academic researchers for pre-clinical testing, pharmaceutical companies will only supply agents when an MTA has been agreed and is in place.

3.1.1.1 Issue

MTAs are used to protect the intellectual property of the material provider who may have invested millions of pounds to develop the material. Christopher's Smile sees this as entirely reasonable for a pharmaceutical company to ensure that it's prototype agents are carefully controlled and are not copied or subject to unauthorised development.

Academic researchers who are developing new treatments for childhood cancer know that no one agent will provide the 'magic bullet' to effect a cure. In fact the approach being taken is to provide personalised medicine to provide the patient with a combination of agents based on tumour biology and not a generic prescription. To develop personalised treatments for childhood cancers, which are all classified as orphan diseases, academic researchers are dependent on new agents being made available to them by pharmaceutical companies. Unfortunately it appears that pharmaceutical companies are only prepared to provide new agents readily on the condition that they are not used in combination with drugs from other manufacturers. Christopher's Smile was made aware of this fact when we questioned the research activities of a funded researcher. We enquired about two agents from different companies being tested in combination. We were informed that neither company allowed their agents to be used in conjunction with any other novel agent not manufactured by their company. These limitations were conditions of supply governed by the MTA. The result of these conditions is that research and the development of potentially lifesaving treatments for children is being stifled.

It should be remembered that research often funded by charities such as ours identifies new markets for new innovative agents. Pharmaceutical companies achieve preclinical testing with full scientific data supplied free of charge. Added to this, should the agent be taken through paediatric clinical trial and a PIP obtained, a further [(2)] 6 months extension of patent protection is gained. The catalyst for this new market and additional profit stream is an academic research team and a small amount of charity funding for preclinical testing, none of which was initiated by the pharmaceutical company. Yet pharmaceutical companies want to tightly control their new agents. We need to ask is whether pharmaceutical companies may be using MTAs to stifle competition? If a biomarker has been identified and another company already has a drug which targets this biomarker, are pharmaceutical companies using MTAs to stop a successful combination being identified which includes another company's product?

Q. Using this approach would it buy the pharmaceutical companies' time to develop their own new agents and produce combinations of their own products?

In the paper *Targeted therapeutics for cancer treatment: major progress towards personalised molecular medicine* Professor Paul Workman and Professor Johann de Bono describe how cancer will be treated using combinations of novel targeted agents. This approach is seen as the future of cancer treatment and offers the hope of a real alternative to the current surgery/cytotoxic agents/radiotherapy that are the only current front line treatments available for children. The paper provides a scientific vision for the future of personalised treatments for cancer but of course does not include any caveat stating that there is a total dependency on pharmaceutical companies' commercial willingness to provide new agents for preclinical testing and the supply of drugs for clinical trials.

3.2 Pre-Clinical Trials

3.2.1 Background

Pre-clinical trials are used to ascertain the efficacy and safety of an agent using both human cell and animal tumour models. Childhood cancers are different in their biology to adult cancers so need separate preclinical testing to determine the effect an agent has in eradicating the disease. Drug candidates for pre-clinical testing are either:

- agents currently approved for use in adults (could be purchased by the laboratory)
- agents that are still in adult clinical trials.

3.2.1.1 Issue

In order to obtain new agents for pre-clinically trialling with paediatric tumour models or cell lines, academic researchers must make a sound case with the agent's manufacturer. The paediatric academic researcher will have either data supplied by the agent manufacturer or any available research papers from adult trials both pre-clinical and clinical, upon which to make a case. Adult clinicians or academic researchers could not provide data about the new agent to their paediatric colleagues as they would be bound by a non-disclosure or a confidentially clause contained in the Material Transfer Agreement. Therefore paediatric researchers are totally reliant upon drug manufacturers or published papers to provide them with data upon which to make requests for new agents.

In our meetings with pharmaceutical companies it was highlighted to us that the quality of the science and reporting from some academic institutions was below a standard which they would expect of a partner. It was indicated that unless a guaranteed standard of science and reporting was assured, agents would not be offered for pre-clinical testing.

There is also the issue of the growing complexity of preclinical trials. Testing multiple agents in combination is highly complex and lengthy. Researchers need a full understanding of how increasing the dosage of one agent will affect the efficacy of the other agent or agents that are used in combination. An increase in the number of agents in the combination results in a proportional increase in the complexity and duration of the preclinical testing. This increase also results in greater cost.

3.3 Paediatric Investigation Plan Process

3.3.1 Background

The Paediatric Investigation Plan (PIP) was created as part of the [3] European Medicinal Products for Paediatric Use (EC 1901/2006). The PIP process is overseen by the European Medicines Agency Paediatric Committee (PDCO). The PIP is intended to ensure that medicines for children have undergone sufficient testing to confirm both their efficacy and safety for use in children. Pharmaceutical companies are rewarded with an additional 6 months extension of patent protection for taking their new agents through the PIP process.

In the United States two acts were passed to promote the testing of new agents for children - Best Pharmaceuticals for Children Act in 2002 and Pediatric Research Equity Act in 2003.

3.3.1.1 Issue

Pharmaceutical companies will not develop any new agents to specifically target and treat a childhood malignancy. The market is small and there would not be an economic return on the development costs. It is for this reason that paediatric oncology drug development is totally dependent on adult drug development.

The [4] 5 Year General Report on the Paediatric Regulation to the EU contains the following paragraph:

"The review of the applicability of a class waiver is also an opportunity for the PDCO to recommend medicines development in paediatric conditions with unmet needs, when the mechanism of action of the medicine justifies development. This was particularly the case for medicines used in adult oncology that can be used, based on their mechanism of action, in different cancers in children with high unmet needs. The PDCO recommended development for a number of medicines. Sadly, no PIP application was received in response to such PDCO recommendations."

The 5 year General Report to the EU on the Paediatric Regulation describes paediatric oncology as an area of high unmet need despite the PIP process having been in place since 2007.

It may suit a drug manufacturer to make a drug unavailable for paediatric pre-clinical testing in order to obtain a PIP waiver. In this case it could be years before an agent is made available to paediatric researchers for pre-clinical testing.

This is typified by the case of the drug Olaparib, a PARP inhibitor. [5] Olaparib was first used in clinical trials in 2005. Olaparib's manufacturer, Astra Zeneca applied to the EMA Paediatric Committee for a class waiver in December 2012. The [6] class waiver was granted thus allowing Astra Zeneca to gain marketing authorisation without the need to carry out a paediatric investigation plan (PIP). The class waiver was granted on the grounds that Olaparib is used to treat ovarian cancer, a disease that does not afflict children. What is strange is that prior to December 2012 a number of papers have indicated that PARP inhibitors may prove [7] beneficial in treating childhood malignancies. Once a waiver has been obtained a pharmaceutical company has removed the dependency on gaining a successful PIP before marketing authorisation can be granted.

The rewards to pharmaceutical companies for obtaining a PIP are not sufficient and a waiver is often sought.

Although model PIPs are starting to be written, the Paediatric Investigation Plan process is seen as a huge burden for any pharmaceutical company especially when there is no guarantee that the agent under trial will be successful. We can understand why the application for a PIP is left until the last moment as there would be no sense in progressing through the PIP process only for a drug to be withdrawn due to safety or efficacy concerns in on-going adult clinical trials.

If we take the case of drugs for personalised medicine, a single agent trialled alone may show little or no therapeutic benefit and yet the drug would need to go through the [8] PIP process if it was to form part of a combination therapy for treating a paediatric cancer. To enable large numbers of single agents to process through the PIP process regulators must be prepared to streamline the PIP process to both reduce the bureaucratic overhead and keep standards high. At present this does not seem a realistic vision.

3.4 Clinical Trials

We see the subject of clinical trials as being one of the major obstacles preventing new treatments being made available to children for front line use. The major issues can be categorised as:

1) Bureaucracy, Complexity and Ethics
2) Funding of clinical trials
3) Clinical trials of multiple novel agents from multiple vendors
4) The number of clinical trials required for personalised medicine

3.4.1 Clinical Trial Setup Bureaucracy, Complexity and Ethics

3.4.1.1 Background

Paediatric trials are seen as high risk simply because they involve children. It must be remembered that some children with cancer are given a prognosis of 'incurable' at first diagnosis and yet we have no fast track process to instigate an innovative trial for these children. Parents seek alternatives abroad in the hope a cure exists for their child. In some cases trials outside of the UK have proven successful while tragically other children are not so lucky and despite taking part in a trial, their battle is lost.

All clinical trials in European Union member countries must comply with the [9] EU Clinical Trials Directive 2001/20/EC. In Europe clinical trials are regulated by national authorities, in the UK it is the role of the Medicines and Health Equipment Regulatory Authority (MHRA) to approve clinical trials.

3.4.1.2 Issue

On the 7th March 2012 John Dalli European Commissioner for Health and Consumer Policy delivered a speech to the European Federation of Pharmaceutical Industries and Associations. John Dalli stated

"There has been a decline in clinical trials in the EU in recent years of about 15%. At the same time, costs for bureaucracy and resource requirements to handle paperwork have doubled, and delays have increased by 90%"

In February 2013 there was an [10] article in the *Daily Telegraph* which highlighted the bureaucratic overhead of clinical trials. While there is much criticism of the level of bureaucracy, politicians and regulators appear

slow to act in order to speed up the implementation of trials. Of course there is no thought for those children whose only hope of life is to enrol on a clinical trial.

While trials need to prove the safety of an agent or a combination of agents there seems to be a double standard when novel agents are presented for trial approval. Novel targeted agents do not possess the horrendous side effects of current cytotoxic treatments which are used 'off label' for children. Yet there is no *'fast track'* process to expedite new treatments to replace cytotoxic agents which are ineffective as treatments for some paediatric cancers and can leave a legacy of issues for those children that do survive.

There is also no provision for novel small scale trials for children who are found to have an incurable malignancy at first diagnosis.

Another factor which hampers paediatric trials is the number of children suitable for a particular trial. Clinical trials of targeted agents require recruits to present specific genetic abnormalities and in order to enrol enough children trials need to be conducted in a number of centres. This causes further delays as before any trial can start, each centre must demonstrate that they have all the personnel and processes in place to conduct the trial.

The clinical trials set up processes do not differentiate between a topical cream for a paediatric skin condition and a novel agent for a currently incurable paediatric malignancy. The current processes do not take into account the urgency of the need for new treatments to be implemented for children with life limiting malignancies or to avoid the horrendous side effects caused by current treatments.

We have to ask why so many barriers to the implementation of clinical trials exist when children whose disease has not been 'cured' by current front line treatments are denied access to the latest targeted drugs. It must also be remembered that even for those children who are cured of their cancer by current treatments, the legacy of issues that they face for the rest of their lives is not acceptable. Safer and more effective treatments are needed immediately and more trials of safer targeted drugs are urgently needed. For those children who have received the worst prognosis, a clinical trial can offer the only hope.

3.4.2 Funding of Clinical Trials

3.4.2.1 Background

Many novel agents have successfully completed preclinical testing for efficacy against paediatric tumour types. All of these agents are either in front line use for adults or currently in adult clinical trials.

In the UK, clinical trial funding for new agents to treat children with cancer comes from 1 of 3 sources:

- Pharmaceutical Companies
- Cancer Research UK through their Birmingham Clinical Trials Unit (charitable funding)
- Cancer Research UK Drug Development Office

In all cases there is a dependency for the agent to be supplied by the manufacturer free of charge. This is different to the United States where in addition to pharmaceutical company funded trials, the National Cancer Institute, a governmental body makes funding available for paediatric clinical trials through the Children's Oncology Group. This has resulted in a greater number of trials being conducted in the United

States and perhaps gives the impression that the United States are more advanced in their scientific knowledge that other countries.

3.4.2.2 Issues

Clinical trials are a mandatory step to demonstrate that a drug is both safe and effective in children and yet there are only two options for funding – pharmaceutical company or charity. With the ever increasing demands for funding from charities for research, the amounts available to fund trials are therefore limited. Charities such as CRUK do not have infinite funds and must prioritise where their funding is targeted. We must not assume that CRUK will automatically fund a clinical trial purely because it is for children. There is no alternative source of clinical trial funding in the UK.

3.4.3 Clinical Trials of Multiple Novel Agents from Multiple Vendors

3.4.3.1 Background

The role of a clinical trial has been to test the safety and efficacy of an agent to treat a defined disease. Trials could be divided into two broad categories:

1. trials of existing agents
2. trials of new agents

The majority of clinical trials for children with cancer involve combinations of existing chemotherapy agents using a randomised methodology targeting a particular disease. The agents are available and their cost is relatively low as the vast majority are out of patent. Even if the trial is successful, no manufacturer is set to gain a huge amount as the drugs are relatively low cost and perhaps produced by a generic drug manufacturer.

Following the drug testing lifecycle, a novel agent must first be tested in a preclinical setting and then undergo 3 phases of clinical trial. For more than one agent to be used in combination a commercial agreement between the manufacturers would be needed to supply their agents for both preclinical and clinical trials.

The issues to be faced are commercial as well as scientific.

3.4.3.2 Issue

Trials of new single targeted agents are starting to be introduced and manufacturers provide the agents for trial. If the trial is successful the manufacturer will reap the rewards, especially if the agent is under patent, and the target market is a large one. If the target market is extremely small as in paediatric oncology then there are few incentives for manufacturers to make their products available for either preclinical or clinical trials.

Should paediatric oncology researchers receive novel agents for preclinical combination testing and the results are promising the next step is to take the combination into the clinic. Before this can be done, a commercial agreement has to be in force to ensure the supply of the agents throughout the lifecycle of the clinical trial.

Q. Why should a manufacturer provide some of their latest agents for testing in combination with other manufacturers products especially if the other manufacturers are their fiercest rivals?

Q. If the target market is extremely small as is the case for paediatric oncology what incentives are there?

Owing to the complexity of preclinical studies of novel agents in combination it is highly unlikely that any manufacturer will allow their agents to go into clinical trial until the product receives full marketing authorisation. If manufacturers decide not to provide their novel agents until this point has been reached then paediatric researchers will need to wait at least five years before drugs available for adults are made available for paediatric preclinical testing.

Due to commercial strategies and small markets the issue is that there are no incentives for pharmaceutical manufacturers to release their products early and certainly not in combination with any products of their rivals.

In the event of collaboration between two or more pharmaceutical companies and an academic partner to develop a combination therapy there is no agreed source of funding for the management of the clinical trial. While the agents themselves may be supplied free of charge by the pharmaceutical companies, the funding of the trial management still needs to be agreed. At present the only avenue available in the UK is CRUK.

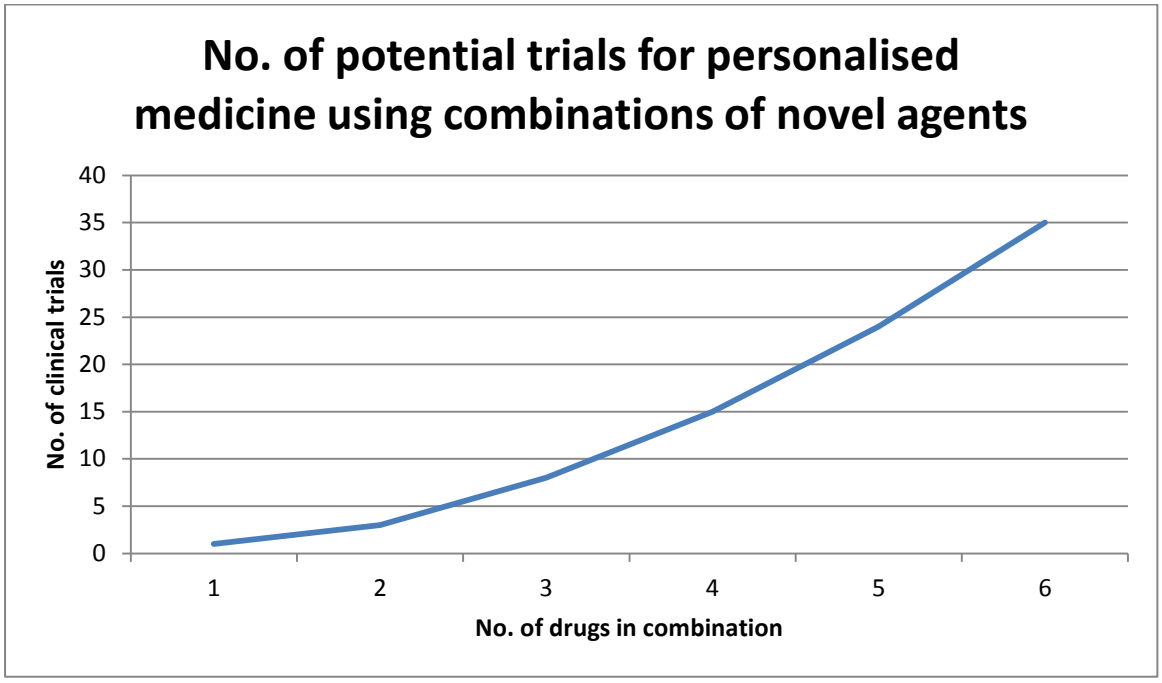
3.4.4 The Number of Clinical Trials Required for Personalised Medicine

Any new protocol or regimen must be tested before it can be authorised as a treatment for children. Today new clinical trials are in progress which include cytotoxic agents over 50 years old. The reason for these trials is to establish whether a new combination of agents will provide better results than current standard protocols or regimens.

If we look beyond clinical trials of single novel agent trials in children to combinations of novel agents, the number of trials that will need to be carried out will be huge. If we assume that 4 agents can be used in any combination to treat a specific patient malignancy, we see that the permutations for different combinations will equal 15.

Combination	Drug 4	Drug 3	Drug 2	Drug 1
1				X
2			X	
3			X	X
4		X		
5		X		X
6		X	X	
7		X	X	X
8	X			
9	X			X
10	X		X	
11	X		X	X
12	X	X		
13	X	X		X
14	X	X	X	
15	X	X	X	X

The above assumption uses 4 possible agents to treat a specific malignancy, if the number of agents is increased the number of trials increases as shown in the graph overleaf.



3.4.4.1 Issue

With the huge overhead of trial set up – documenting the trial, training, patient information sheet production, ethical committee approval, trial centre implementation, the current model for trial setup is unsustainable if personalised medicine is to be introduced for children within the next 10 years.

It must also be remembered that some paediatric malignancies are extremely rare so obtaining sufficient trial participants will be an issue.

A new approach is needed.

3.5 New Drug Availability for Childhood Cancer

3.5.1 Background

To provide personalised medicine for children with cancer, drugs will be needed that:

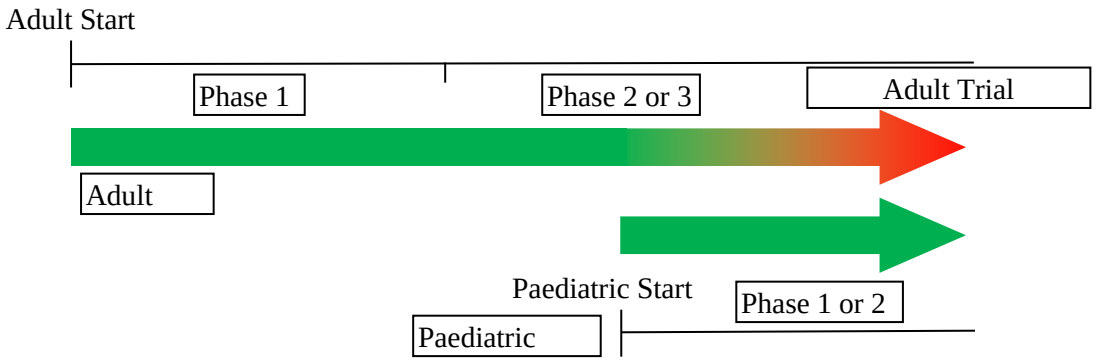
- Target gene abnormalities which are common to both adult and paediatric tumour types
- Target gene abnormalities which are specific to a paediatric tumour type.

Paediatric oncology researchers rely on the availability of new drugs that have been developed to target specific gene abnormalities in adult malignancies which have also been identified in paediatric tumours. Therefore there is a dependency on adult research and drug development. As paediatric tumours are different in their biological composition to adult tumours, different drugs to those developed for adults are also needed. No pharmaceutical company will develop a drug exclusively to treat a paediatric tumour type. The reasons for this are purely economic. The cost of developing, pre-clinically testing and trialling a drug would far outweigh the potential profits from such a small market. The EU do provide incentives for [(11)] 'Orphan Drug' development and for carrying out Paediatric Investigation Plans (PIP) but these incentives are not enough and to date no targeted biological agent has been developed to exclusively treat a paediatric malignancy.

3.5.1.1 Issue

Pharmaceutical companies generate their profits from patent drugs. During the patent period – typically 20 years, pharmaceutical companies must recoup their development costs and provide for investor profit. Pharmaceutical companies are not charities and they are driven by the need to develop new drugs and improve their shareholder value. It must also be remembered that pharmaceutical companies spend hundreds of millions if not billions of pounds worldwide in their global research for new drugs. If pharmaceutical companies did not make a profit then this research would not happen. It is therefore essential that pharmaceutical companies make enough profit to fund their on-going research and keep their shareholders happy. In order for pharmaceutical companies to generate the desired level of profit during the patent period of a drug, both the sales volume and the price must be high as possible.

Often drugs developed to treat a common adult condition are pre-clinically tested for efficacy on less common paediatric diseases. Some of these tests provide encouraging results prompting the case for clinical trial. Such trials always lag behind their adult counterpart enabling the paediatric trial to obtain early warnings of any unforeseen side effects which may seriously impact patient safety. However some adult trials founder simply through the lack of efficacy.



The adult drug in the above case may have been developed to treat a common disease for which there is a huge global market. The paediatric trial, initiated by either academia or a pharmaceutical company, may be for an uncommon disease which has a tiny global market. Should the adult trial fail and the paediatric trial be successful the pharmaceutical company can benefit from orphan drug status but only for treatment of the less common paediatric disease. If the orphan drug and PIP incentives do not compensate for the entire costs of the drug's development or the production and distribution costs of extremely small quantities, the drug would become a financial liability to the pharmaceutical company. Financially it would be better to withdraw the drug and write down the development costs as a loss than to continue even with orphan status. There would be little point in continuing any paediatric trial and if successful, taking the drug to market.

The biggest loss to a pharmaceutical company would be the withdrawal of an adult drug with a globally registered patent. The patent would continue to be in force with an extremely small paediatric use drug sales volume. If it were subsequently found that the drug could be used for another high volume adult malignancy years later the time remaining on the patent, and hence the time to make a healthy profit would be drastically reduced. It would be less costly to withdraw the drug completely. Evidence that these practices are in place does not exist as pharmaceutical companies demand confidentiality from researchers,

administrators and clinicians. This is entirely reasonable as leaked news on the progress of a new drug could affect a company's share price. This is also controlled by financial dealing legislation worldwide.

The losers of course in this situation are children with cancer. If pharmaceutical companies are reluctant to supply new drugs for paediatric testing until adult trials are extremely well advanced – end of Phase 2 or start of Phase 3, drugs would exist but they would remain out of reach. There is no incentive to supply the following to academic researchers:

- drugs that have failed efficacy targets in adults
- drugs that have not been pre-clinically tested
- drugs for which a patent has not been registered.

Some pharmaceutical companies do publish their past clinical trial data. This is a new initiative and we are not currently aware of the benefits such availability of data brings but we do agree with this open approach.

3.6 Availability of New Technologies

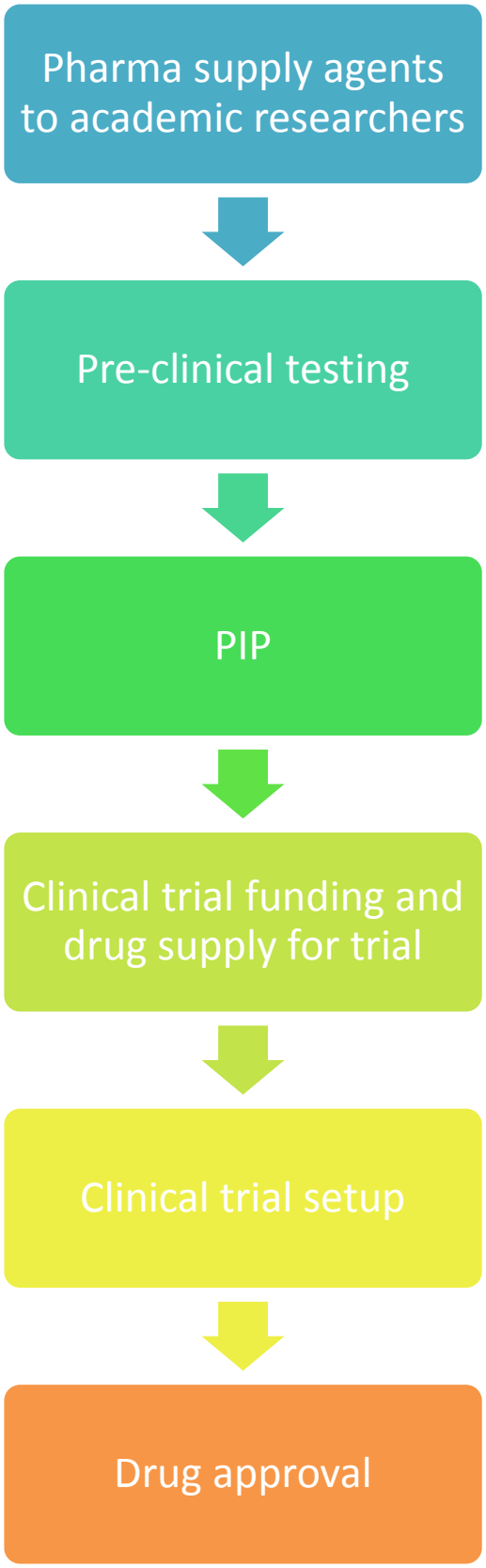
3.6.1 Background

In 2001 the cost of sequencing a human genome was in the region of $100M. In the intervening years the cost of sequencing a human genome has fallen below $10,000 and continues to fall. This dramatic drop in cost has been enabled by the development and introduction of new technologies. These new technologies enable researchers to analyse genetic abnormalities in cancer far quicker than before. The low cost of analysis is allowing clinical trial participants to be chosen not by their disease but by the specific genetic abnormalities present in their tumour.

3.6.1.1 Issue

In order to standardise the identification of candidates for clinical trial by the genetic abnormalities present in tumours, centres must possess the new technology analysis equipment. This equipment, the personnel, the on-going equipment support contracts all come with a cost. This is at a time when health authorities are trying to reduce their budgets. Genetic analysis is an essential component of personalised medicine yet no UK governmental funding for paediatric molecular pathology has so far been allocated.

4 Where we want to be



Pharma invites academic researchers to test any of their available agents with no testing pre-conditions set by MTAs.

Adequate charity funding available to develop in vitro and in vivo cell and tumour models. Adequate funding for single agent and combination pre-clinical testing.

Requirement for PIP based on agent mechanism of action. PIP process requires only Phase 1 trial detail to start. Subsequent detail needs to be added as soon as practicably possible.

Funding for clinical trials available from central independent authority. Pharmas agree to supply novel agents for single agent and combination trials.

Size of trial would influence process. Trial participants selected for their suitability based on tumour biology. Methodology would allow for personalised suite of agents used in combination from a defined selection of agents.

Following 3 phases of clinical trial and subsequent results publication, a defined selection of agents used in personalised combinations gain approval by the regulatory authority.

5 Proposals for Solutions

5.1 Material Transfer Agreements

5.1.1 Proposal for solution

With immediate effect, pharmaceutical companies provide their agents to academic researchers with no limitations on using them in combination with another company's products.

We know this is not a proposal that the pharmaceutical companies will welcome but the stifling of scientific progress and the delaying of new treatments due to commercial interests is ethically wrong and unacceptable.

We propose that MTAs are used to define the quality of the science and reporting expected by the pharmaceutical company supplying the agent.

5.2 Pre-Clinical Trials

5.2.1 Proposal for solution

To enable early paediatric pre-clinical testing of novel agents, an incentive should be offered to pharmaceutical companies. This incentive should take the form of another three months marketing exclusivity added to the six months for completing a PIP. Although this sounds generous, by making a new agent available to paediatric researchers at the end of successful adult Phase 1 trials would be a huge advantage. Currently paediatric researchers have to wait years after adult Phase 1 trials before some drugs are made available to paediatric researchers. An example of this is Olaparib.

Academic researchers also have their part to play. If pharmaceutical companies were to make their latest agents available earlier, the research community should ensure that the quality of the science and reporting meets the standards required by the pharmaceutical companies.

5.3 Paediatric Investigation Plan Process

5.3.1 Proposal for solution

We propose amendments to the PIP process which result in a lower administrative burden in the early phases of a trial. Class waivers must only be granted where the agent mechanism of action does not treat any paediatric disease

PIPs which are not completed should be reviewed to ensure a paediatric trial has not been ceased purely due to poor efficacy in the adult trial. In such cases where the paediatric results are positive, the pharmaceutical company should be approached with a view to finding a way of continuing the paediatric study.

5.4 Clinical Trials

5.4.1 Proposal for solution – Clinical Trial Setup Bureaucracy, Complexity and Ethics

To enable more trials a simpler model is needed. Professor Paul Workman in a recent BBC Radio 4 interview stated that clinical trials needed to be smaller. Professor Workman was referring to trials of innovative targeted agents in adults but the same is also true for children. Due to the low numbers of prospective candidates for paediatric trials it is our belief that trials should start in a single centre with the children brought to the trial, not the trial to the children.

Regulators should work with academic researchers, clinicians and pharmaceutical companies to develop standard trial methodologies for combination treatments. Patient information sheets should be standardised and once a template has been approved there should be no need to reapprove every new patient information sheet for every trial. Parent representatives could be included in ethics committee reviews of paediatric trials. Trial management should also be standardised to provide regularised reporting and metrics. If in the future we see the need for a high volume of trials there should be no need to treat each trial as an individual study and continually 'reinvent the wheel'?

It may take some time to produce a standardised format for paediatric clinical trials but if clear objectives for change are agreed and set in place there should be no reason why trials in the future cannot be quicker to implement, provide high quality monitoring, management and reporting.

5.4.2 Proposal for solution – Funding of Clinical Trials

There is an urgent need for a clinical trial funding and management body in Europe using the same model as the US National Cancer Institute support for the Children's Oncology Group. Currently in Europe clinical trials are co-ordinated by national bodies such as the UK Children's Cancer and Leukaemia Group (CCLG). A better approach would be to instigate pan European clinical trials funded and managed by a single body.

An alternative proposal is an iterative approach to funding where governmental funding is used for small scale first and second phases and if successful, Pharma would then fund the third phase. Statistics show that the vast majority of clinical trials fail in either the first or second phases so the risk for Pharma is relatively low. It must also be remembered that the majority of paediatric trials use drugs that have either gone through the clinical trials process for adults or are at an advanced clinical trial stage in adults.

Personalised medicine for children will require large numbers of successfully tested combinations of targeted agents.

5.4.3 Proposal for solution – Multiple Novel Agents from Multiple Vendors

In order to introduce personalised medicine for children targeted agents must be trialled in combination. While some combinations will consist of agents from one manufacturer, it is likely that most combinations will consist of agents from two or more manufacturers. In these cases it is highly unlikely that a quick commercial agreement would be put in place to agree to fund a trial and the best hope is that the agents would be provided courtesy of the manufacturers. This leaves the funding of the trial management and reporting.

We propose that funding for paediatric clinical trial management is provided by the European Union but only for trials that provide treatments for fatal diseases with all agents included in the trial having successfully gone through the PIP process. Paediatric oncology trials of novel agents would be within this scope.

We recommend that a working group be formed immediately to make proposals for the future funding of multi-vendor trials. The working group could consist of the following:

- EMA (PDCO)
- Pharmaceutical Industry
- Academic Researchers
- EU Heath Committee
- An independent representative who ensures progress is made

We recommend that charities are not involved in this working group as clinical trials should not be constrained by the availability of charity funding.

5.4.4 Proposal for solution – The Number of Clinical Trials Required for Personalised Medicine

As more targeted agents are made available for preclinical and clinical trials the number of agents used in combination will increase. As each combination of agents will need to be trailed, the advent of personalised medicine introduces the issue of a huge increase in the number of trials needed. As paediatric cancers are less common than adult cancers the number of eligible children presenting the specific genetic abnormalities required for trial recruitment may be extremely low.

We therefore propose that trials must be smaller, held in an extremely small number of centres globally and that children are moved to the trials. By splitting the world into zones such as:

- Europe, Middle East and Africa
- The Americas
- Northern Asia
- Southern Asia & Australasia

A single centre in each region could run the trial and by moving children to the trial, enough recruits hopefully could be found, even for the rarest cancers.

This approach would need international collaboration and may provide a lifeline for children with cancer globally.

Trial costs would need to be met by such governmental bodies as the European Union, the US National Cancer Institute and by central funding in Asia and Australasia.

Planning a solution for the future will help children with cancer globally.

5.5 New Drug Availability for Childhood Cancer

5.5.1 Proposal for solution

It is in the interests of all parties – pharmaceutical companies, academic researchers, clinicians and patients that effective, safe drugs are discovered as quickly as possible to combat those diseases which have the

worst prognosis – especially in the case of children. Before we look at the proposal it is worth looking at the WIIFM (What's In It For Me) for each party with relation to new drugs gaining approval.

Pharmaceutical company - the culmination of years of investment, the chance to recoup their investment, provide shareholder return and provide funding for future research and development.

Academic researchers – the realisation that years of research have proved successful

Clinicians – can add a new and powerful weapon to their armoury in the fight against disease and give patients a better outcome.

Patients – a chance of survival where previously their chances of life would have been slim.

Each group has different interests but all would benefit from a new successful drug. A high proportion of new drugs however do not proceed beyond Phase 2 for a variety of reasons.

Until recently the results of clinical trials have been based upon the comparative patient response to a new drug or a current drug/placebo. The selection of the trial patient candidates has been random and based upon disease type and stage. Genetic analysis of potential patient candidates has not been used for a variety of reasons but notably the availability of new technology to perform this analysis in a timely manner. Past trials have failed due to perceived efficacy of a new drug versus an existing drug or placebo. In the past there has been little or no analysis as to the reasons why a new drug was successful for a small group of trial participants based on their tumour genetics. When trials for a drug cease due to poor efficacy for example, the question is raised "what happens to the drug now?" Academic researchers may have spent years or even decades searching for a drug target. Pharmaceutical companies could have taken the academic research and spent years and huge sums developing a drug. There is also the matter of patents. Prior to pre-clinical testing a drug patent would be registered by its developer. Should a drug not meet its efficacy targets during clinical trials, the owning pharmaceutical company would have no option but to withdraw the drug. The drug would sit in a pharmaceutical company inventory, the patent time ticking away, until either an alternative use has been found or the patent has been withdrawn. So after many man years' effort and huge monetary sums expended, the result is 'drug withdrawn'. The number of 'withdrawn drugs' in pharmaceutical companies' inventories can only be estimated. Clinicians involved in the trials have to revert to existing drugs which may be extremely toxic or whose efficacy is limited and finally there is no new hope for patients.

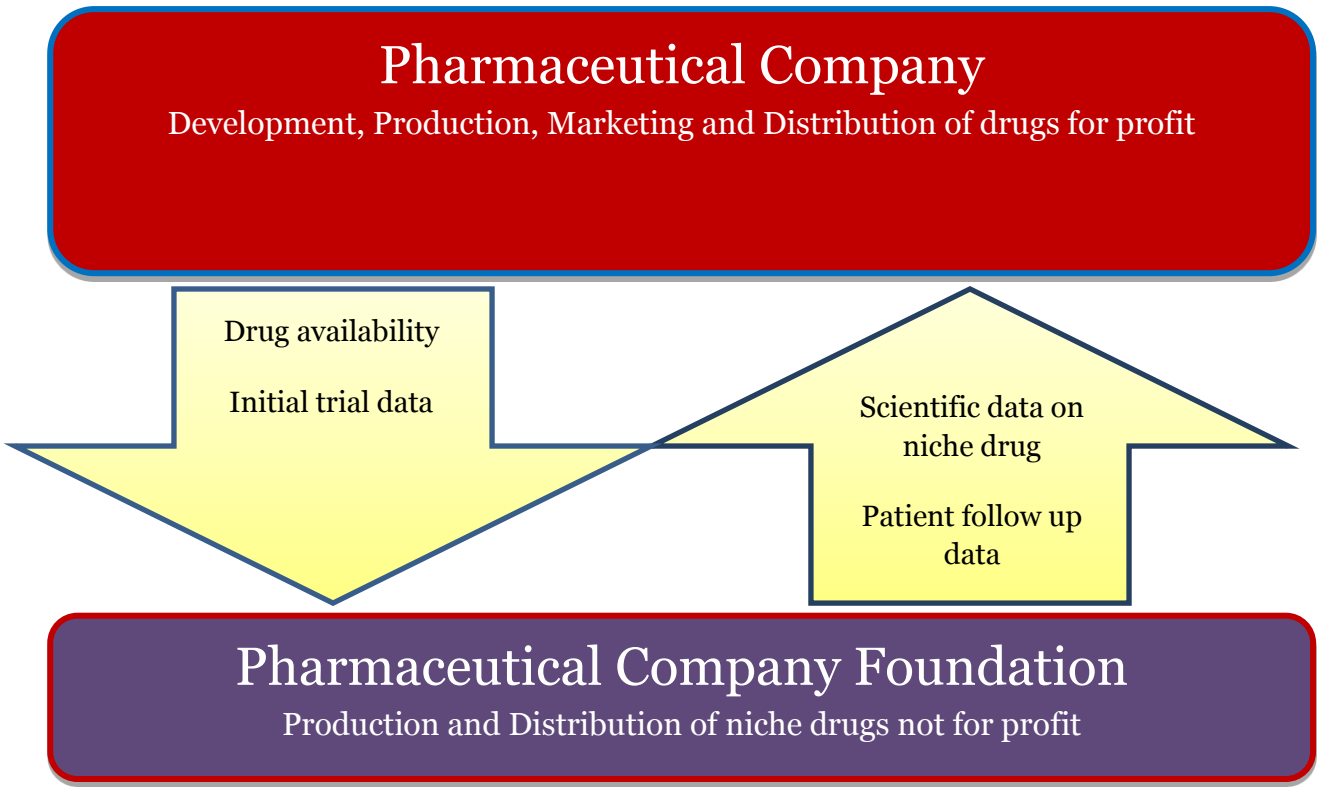
In the case of cancer it is accepted that many drug targets are yet to be found. For the drug targets that have been found, the race is on to develop safe effective drugs which address the genetic abnormality but leave healthy cells untouched. For less common diseases we need to ask what incentives are there for pharmaceutical companies to undertake this work if the sales volumes are extremely low. Although Academics, Clinicians and Patients can identify clear benefits, pharmaceutical companies may not benefit at all. Development and trial costs massively outweigh potential revenues due to the small market segment which would purchase these niche drugs. There would be no value giving a failed drug together with its patent to academic institutions for development, trial and subsequent production and distribution, as academic institutions are not pharmaceutical companies but institutes of learning.

A new tactic is needed to encourage pharmaceutical companies to open their inventories to academic research institutions thereby enabling the testing of 'dormant' drugs against rare diseases utilising the latest technologies to select the most appropriate trial patient candidates based on tumour biology. We propose

that each pharmaceutical company creates a non-profit making foundation for the sole purpose of managing niche drugs that have a small market. This proposal would therefore allow pharmaceutical companies to transfer the drug manufacture and distribution to its foundation and must allow for the retention of the patent. One condition of this proposal is that paediatric academic researchers would gain access to the drugs. The foundation would be its own legal entity separate from the pharmaceutical company.

In order to provide an incentive to pharmaceutical companies to accept this proposal the patent laws must be changed. The change needed would allow drugs that were produced not for profit and for the public good to have patent registrations continue at no cost and the 'patent clock' stopped. This could be achieved using a similar process to that of the [(12)] 'Supplementary Protection Certificate for Medicinal Products'. Instead of applying for a certificate to extend marketing protection for a defined time period, a certificate could be issued to a pharmaceutical company who had transferred the management of a drug to its non-profit making foundation. On issuance of a certificate the patent clock would effectively stop. Should the situation arise where the drug returned to a for profit basis the pharmaceutical company would return the certificate. This would allow the pharmaceutical companies to take the drug back if it proved to be an effective treatment for a common disease. The remaining patent life would be unchanged from when the drug was passed to the foundation for management.

There would be the added advantages for the pharmaceutical company to receive scientific data on the drug from trials and on-going patient follow up.

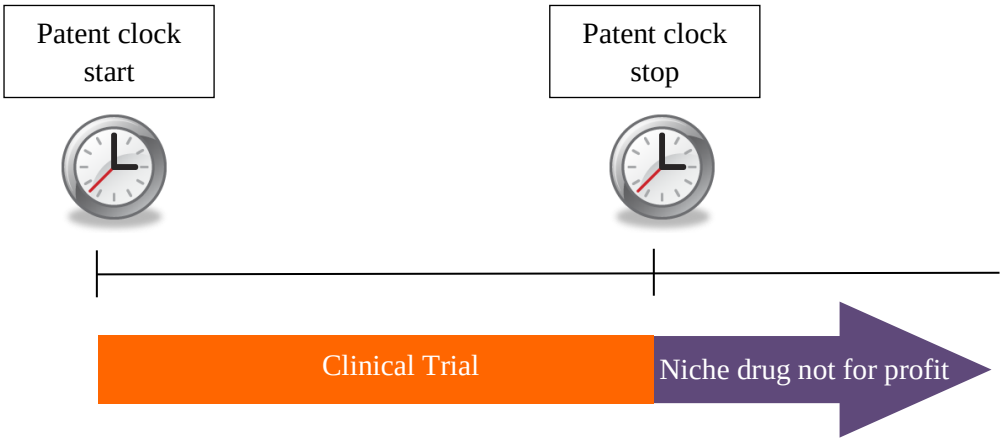


We are fully aware that this proposal would need legislative change which would potentially be a lengthy process. Some parties would see this initiative benefiting pharmaceutical companies. We think this approach is the best way to incentivise the pharmaceutical industry to open up their inventories for the evaluation of agents for low volume usage.

5.5.1.1 Scenario 1

A drug is trialled to target a biomarker discovered in a common disease. The drug does not meet efficacy expectations but a parallel trial to target the same biomarker frequently found in a childhood cancer shows the drug is effective. The drug is never used to treat the common disease.

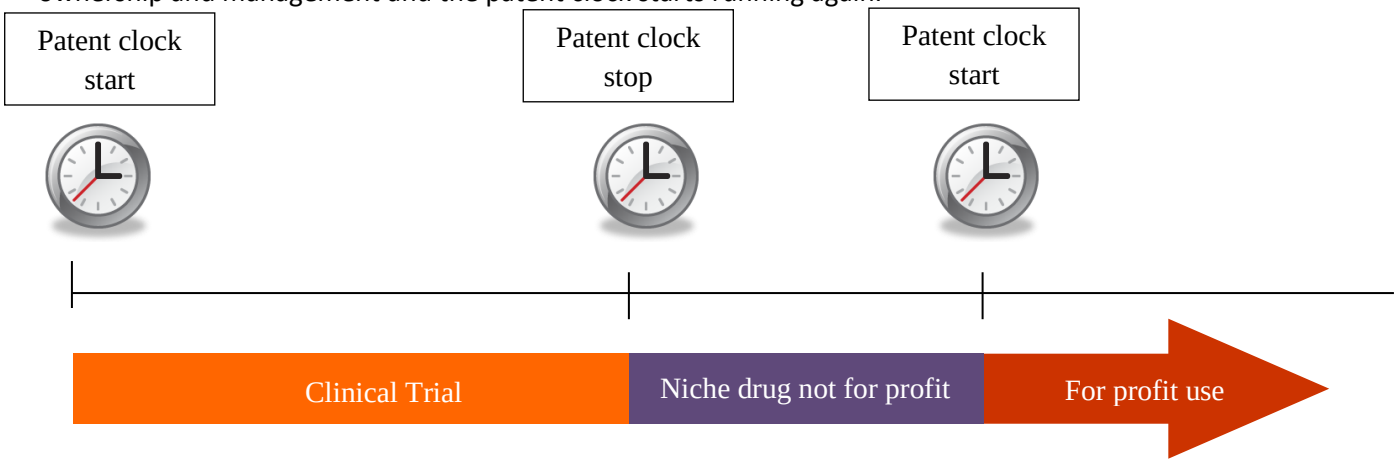
In this scenario the trial for the common disease is stopped. The drug is handed over to the Foundation for ownership and trial management. At this point the patent clock stops and the time elapsed since patent registration does not change for as long as the drug is managed by the foundation. The trial for the childhood cancer continues under the management of the foundation. PIP approval of the drug is sought while under the management of the trial and if granted the drug is given 6 months extension of patent protection. This is academic because if the drug remains under the management of the foundation the patent will stay in place and never expire.



5.5.1.2 Scenario 2

A drug is trialled to treat a common disease, does not meet efficacy expectations but a parallel trial to treat a rare disease shows the drug is effective. The drug is used to treat rare diseases for a period of time and then following a successful trial used to treat a different common disease.

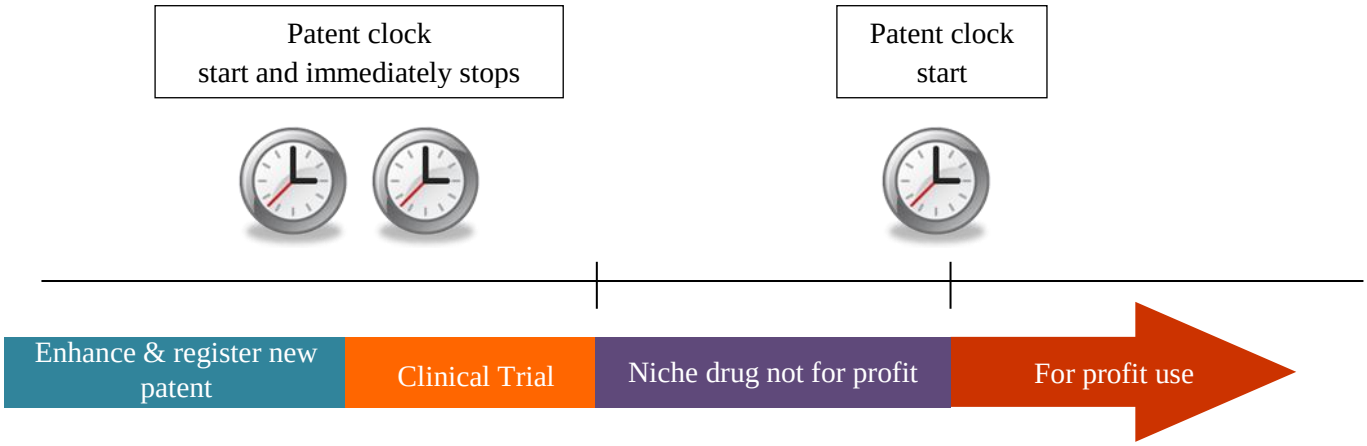
In this scenario the trial for the common disease is stopped. The drug is handed over to the Foundation for ownership and trial management. At this point the patent clock stops and the time elapsed since patent registration does not change for as long as the drug is managed by the foundation. The trial for the rare disease continues under the management of the foundation. PIP approval of the drug is sought while under the management of the trial and if granted the drug is given 6 months market exclusivity. After a number of years the drug is trialled against a common disease. The pharmaceutical company and not the foundation funds this trial. Following the successful trial, the drug is brought back to the pharmaceutical company for ownership and management and the patent clock starts running again.



5.5.1.3 Scenario 3

In this scenario an old drug whose patent has expired is supplied to an academic research institute by the foundation. The academic research institute conduct pre-clinical trials against a rare disease and find that the drug needs enhancing to achieve better efficacy. The academic institute work with the foundation to enhance the drug and the patent is registered by the pharmaceutical company. As this is a new patent and the management is being undertaken by the foundation, the patent clock immediately stops. The foundation funds and manages the clinical trial and the PIP process. As a PIP was undertaken, 6 months extension of patent protection is granted.

After a number of years the drug is trialled against a common disease. The pharmaceutical company and not the foundation funds this trial. Following the successful trial, the drug is brought back to the pharmaceutical company for management and the patent clock starts running. However, as the drug had never been managed by the pharmaceutical company the full 20 years patent life remain and the additional 6 months extension of patent protection are added giving 20.5 years of exclusive sales.



5.5.2 Not for Profit Drug Pricing - Factors

As niche drugs would be supplied not for profit while managed by a pharmaceutical company's foundation, the factors used to determine pricing would be different to those used when determining pricing for a 'for profit' model.

Manufacture would be small scale and would not need the high volume facilities that are used to manufacture high sales volume drugs. Raw materials may have a proportionally higher cost due to the lower volumes required. A simple internet search for "limited market drug manufacturing" provides a number of companies who specialise in low volume drug manufacture.

Distribution could use the same model that is used for clinical trials. There are a surprising number of specialised clinical trial global logistics companies, any of which could be engaged to provide storage, process orders and manage distribution to the point of need. As volumes would be very small one or two distribution centres may be needed globally.

Running costs – staff, facilities and governance for the foundation would need to be factored into the pricing.

An additional supplement could be included in the price of the drug in order to provide funding for drugs to be supplied for not-for-profit trials. Funding for the management of such trials would need to be found from another source. In this way the not-for-profit foundation could supply drugs for trials as the need arose. It is not envisaged that this cost would be huge as trials would need to be small scale as the number of trial participants would be small.

The greatest difference between drugs produced 'for profit' and 'not for profit' would be the inclusion in the price for sales and marketing costs. We know that paediatric oncologists form a global close knit community and that even closer groups exist consisting of specialists in a particular disease. These groups are in constant communication and any new breakthrough or scientific paper is quickly consumed by group members. Therefore if a treatment regime was developed and gained subsequent regulatory approval, the

group members would be immediately aware and would not need to be bombarded with pharmaceutical marketing material promoting a new drug.

5.6 Availability of New Technologies

5.6.1 Proposal for Solution

Sufficient funding must be secured to procure, operate and maintain the latest high technology equipment for the analysis of patient tissue. A standardised approach is needed to achieve economies of scale. By selecting a standard range of equipment types for all paediatric oncology clinical trial centres, costs could be significantly reduced. The issue remains though as to the source of funding. While charities could provide a sizeable amount of funding this would be inconsistent across countries, so a centralised funding source would be needed. This funding source would need to be governmental in origin.

6 Conclusions

There are many facets of childhood cancer treatment we have encountered since Christopher died in 2008. Our conclusions are that the scientific knowledge has forged ahead and the willingness of pharmaceutical companies, regulators & politicians for change has not altered as each have their own differing agendas.

6.1 Pharmaceutical companies

The only way pharmaceutical companies can prosper is to invest in the development of new products and provide a financial return for their shareholders. Bringing new products to market can cost hundreds of millions of pounds. It is therefore perfectly understandable for pharmaceutical companies to target markets which will provide a healthy return on their investment. Thankfully cancer in children is not a common disease which means that as a very small market paediatric oncology is not specifically targeted for new product development by the pharmaceutical companies. Regulations such as the European Medicinal Products for Paediatric Use (EC 1901/2006) (EU) and the Best Pharmaceuticals for Children Act in 2002 and Pediatric Research Equity Act in 2003.(US) have encouraged pharmaceutical companies to test their products in paediatric populations and produce a paediatric formulation where required. Many oncologists that we have spoken to see this stick versus carrot approach as not providing the necessary incentives needed to encourage the pharmaceutical industry to develop, trial, manufacture and distribute drugs for small markets.

6.2 Regulators

In 2010 we met with members of the paediatric committee of the European Medicines Agency, a European Union body, in Canary Wharf, London. We presented a list of points which we saw as opportunities for change. The response we received was that the EMA was a regulatory body and that they did not make the rules; just ensured the rules were carried out. We left not knowing if the meeting was a waste of everyone's time. It seemed there was no impetus to expedite the introduction of new safer treatments for children with cancer. If regulators really want to ensure children are treated with safe and tested treatments they should shed their passive role and speak out for the early introduction of targeted treatments. It is nothing but hypocrisy for the regulators to state they want children to be treated with safe treatments when they know that every day children with cancer are treated with off label drugs that would not meet the strict criteria needed to meet today's paediatric approval requirements.

6.3 Politicians

To encourage pharmaceutical companies to produce and distribute drugs for extremely small markets there need to be real incentives offered. A change in the patent laws would allow pharmaceutical companies to provide drugs on a not for profit basis in return for a halting of the 'patent clock'. This would allow pharmaceutical companies who would have spent millions in development and testing to make their drug available for a niche use. Pharmaceutical companies are commercial organisations which must make a profit to fund further development and shareholder returns. Currently there is no real incentive to manufacture for a tiny niche market. This must change if a broader range of niche drugs is to be made available for children.

The cost of any such change in legislation would be negligible. In fact the true cost of childhood cancer has never been estimated. There is a cost regardless of treatment outcome. If a child survives often there is the cost of a lifetime of issues caused by current treatments. When a child dies there are social costs which are normally hidden. Frequently the loss of a child results in marriage and family breakdown, disrupted education and emotional issues for siblings. The cost of treatment using current therapies is huge with the toxic effects of chemotherapy causing extended periods of hospitalisation and the use of even more drugs to counteract side effects.

The introduction of new therapies will mean fewer side effects, shorter periods of hospitalisation, fewer long term health issues and hopefully a higher survival rate resulting in fewer children losing their lives.

6.4 Clinical Trials

In order to introduce personalised medicine for children with cancer there needs to be a step change in the number of clinical trials run. If every drug combination needs to be trialled, a radical rethink is essential. The clinical trial planning and implementation must be speeded up while still meeting the strict regulatory requirements essential for the continued safety of patients. There is no reason why this cannot be addressed and organisations such as the MHRA should start to engage with pharmaceutical companies, parent organisations, academic researchers and clinicians to develop new approaches.

The one limiting factor for paediatric oncology trials is recruiting suitable participants for each trial. Thankfully paediatric cancer is not common. If a trial is for a combination of drugs targeting a specific combination of genetic abnormalities, the number of prospective trial participants will be tiny. There must be a change in attitude towards clinical trials. Trials must be smaller and the first two phases should be run in single centres in a co-ordinated approach in order to run as many simultaneous trials as possible. In Europe this would mean that families would have to cross borders to participate in a trial. Today some children travel thousands of miles in the hope of a cure when all avenues have been exhausted in their home country. When you are faced with losing your child, travelling to a foreign country to participate in a high quality trial is not an issue.

What is the role of 'ethics committees'? Are they in place to ensure that research and clinical trials are being conducted in an ethical manner? If this is the case why are the ethics committee members not clamouring for change? If ethics committee members included childhood cancer survivors and parents perhaps their emphasis would change.

7 Final Conclusion

This document has been written from the perspective of parents who have fought to save their only child from cancer, who having lost the greatest and hardest battle of their lives subsequently continue to battle to help save other children from this disease. Many areas of concern highlighted in this document which have been 'discovered' in the past four years, none of them are insurmountable. The key requirement is a willingness to embrace changes with the enormous potential to make a significant improvement in the lives of our children.

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