Making European regulations work for children with cancer

A set of proposals by parents, survivors and their supporters

Cancer remains the primary cause of death by disease of children and adolescents in Europe, yet investment in research into childhood cancers lags far behind that for adults. A few basic changes to European law, however, could transform the situation and harness the major advances that have been made in biological science for the benefit of children. We are, therefore, calling for a specific set of reforms to be made to the Paediatric Medicines Regulation without delay.

Great strides have been made in treatments for young people with cancer over the past 50 years and, in the developed world, roughly 80% of children now survive the illness. However, many suffer long term effects from the medication they receive and cancer still remains the most common non-accidental cause of death in young people in Europe. Moreover, there is a significant group of children's cancers for which overall survival rates remain stubbornly below 25%. For conditions like high risk neuroblastoma, metastatic sarcomas or pontine gliomas, virtually no improvements have been seen for decades. Overall, 6000 children and young people under 24 still die of cancer every year in Europe (Vassal, 2014).

Researchers acknowledge that the problem is not just medical but also economic (ITCC, 2012). Pharmaceutical companies consider the adult population their key customer base. Childhood cancers have been neglected as they are made up of a series of predominantly rare illnesses, virtually none of which offer a lucrative market for commercially developed drugs. (Saint-Raymond et al, 2012))

An important step in confronting this problem was made with the introduction of the Paediatric Medicines Regulation (or PMR) in 2007. This piece of European legislation promotes research into all children's illnesses. However, with regard to cancer in particular, the PMR has not lived

up to the promise it held out to provide them with safe and efficient medicines. This statement identifies particular flaws in the Regulation and makes proposals for how they should be fixed.

Remove waivers

The central requirement of the Regulation is for the industry to screen every new adult product they develop for its potential paediatric use (i.e. for the treatment of children). At the first stage of research into a drug for adults, a Paediatric Investigation Plan or PIP must be submitted to the European Medicines Agency (or EMA.) However, if the treatment being researched is for an illness that only occurs in adults, e.g. ovarian cancer, then the drug company can apply to have the Plan set aside or *waived*.

Although children's cancers are usually different from those experienced in adulthood, advances in molecular biology have shown that there are important connections in terms of underlying biology. Indeed over the past four decades, 90% of drugs successfully given to young people with cancer have been used for different tumour types in adults (Vassal et al, 2013).

The example of crizotinib is instructive. This drug is now authorised in Europe for the treatment of non- small cell lung cancer (NSCLC). Research on crizotinib began as recently as 2007, but its development in children was waived in 2010 on the grounds that "NSCLC does not exist in children". This was despite the fact that the drug was known to be active *at a molecular level* in a number of childhood cancers, including lymphoma, something that has been confirmed since in trials conducted in the United States (ITCC, 2014).

In the first five years of the Regulation, twenty six adult drugs with a potential relevance to childhood cancers were developed, but over half of these had paediatric waivers (ITCC, 2012).

In response, the Institute of Cancer Research has made this statement:

We strongly support replacing the class waiver system with one that looks at the mechanism of action of the drug, and feel that this would substantially increase the number of paediatric trials for potentially very important drugs for childhood cancers.

(ICR, 2014)

Make Paediatric Investigation Plans 'smarter'

Removing the waivers where the *mechanism of action* of the drug is relevant to young people's cancers would generate a powerful new wave of research that would allow children to reap

some of the benefits adults have already experienced. However, researchers accept that such a process must be orderly. Competing companies, for example, often develop comparable drugs and if PIPs were randomly introduced for all of them, this might result in too many researchers chasing too few patients (Adamson, 2013).

A Platform[1] of key stakeholders in Europe however, has made a number of proposals on how the process might be structured and these could be built into the Regulation. For example, a centralised European database of molecular targets in children is being established to which new agents could be matched as they become available. Prioritisation of drugs would involve all stakeholders. The European Medicines Agency (EMA) could facilitate such co-operation.

The Platform acknowledges, as do most of the research community, that Paediatric Investigation Plans (PIPs), under the current requirements, are too rigid and the complexity of the requirements in some cases actually delay research. A detailed plan of all three phases of the trial has to be agreed by the EMA, even before preliminary paediatric testing of the drugs has been carried out (Adamson, 2013). The Platform advocates a 'lifecycle' approach and that initial research could be conducted prior to the submission of a PIP and the plan could be periodically revised as understanding of the therapy developed.

Do not abandon drugs that show promise

In addition to the waivers, there are other weaknesses in the Regulation that need to be included in a package of reform. For example, even if a PIP is agreed, it can be abandoned if the adult trial is unsuccessful. Investigation of IGF 1R inhibitors for bone cancer in the young, for example, was dropped because the corresponding trials into adult cancers proved inconclusive. This is despite the fact that 'significant benefit' has been demonstrated in 10% of children taking part in trials of this new agent.

Make age of entry to trials flexible

There are also issues around the legal distinction made between an adult and a child. A PIP may go forward where a cancer occurs in both adults and children but, as with melanoma, the number of young people with the illness may be so small as to make a distinct Paediatric Plan impractical. The solution here would be for the age of entry to adult trials to be made more flexible, based on factors of biology and safety, rather than arbitrary notions of maturity.

Make incentives and sanctions stronger

Reforms of this kind could give a long-awaited boost to childhood cancer research in Europe which, in turn, would accelerate innovation across the Atlantic and beyond. However, if Industry is to be engaged, it must be given reasons to do so.

The reward that is currently offered for completing a PIP is six months' exclusive access to the market. However, so far, this has generated little commercial interest at least in the field of anticancer drugs. In particular, small bio-tech companies, which often operate on shoestring budgets, may need long-term financial incentives if they are to engage with paediatric research. As children's cancers are different from adult cancers, research on specific pediatric drugs should also be encouraged.

If there is a lack of incentives for the commercial companies, there are also few effective sanctions placed upon them. Researchers report that PIPs are routinely submitted long after deadline because there are no penalties (ITCC, 2012).

The lives of children depend on paediatric medicine in Europe being put on a proper legal footing. We therefore propose:

- no waivers if the mechanism of action of an adult drug is relevant to a childhood condition
- support for a European database of molecular targets in paediatric cancer
- multi- stakeholder prioritisation of drugs
- facilities for the EMA to encourage collaboration between drug companies
- a 'lifecycle' approach in which early clinical trials are conducted before PIPs are submitted and plans can be revised in the light of evolving data
- PIPs that show significant promise to be carried forward even if the corresponding adult trial is abandoned
- encourage the voluntary development of specific pediatric drugs
- flexible ages of entry to adult trials based on biology and considerations of safety

All of the above to be backed by strong incentives and sanctions.

To achieve this a CHANGE to the Paediatric Medicines Regulation is required.

NO MORE WAIVERS – FIGHT CHILDHOOD CANCER NOW

[1]The multi-stakeholder **CDDF ITCC ENCCA SIOPE Paediatric Platform**

Jargon buster

CDDF Cancer Drugs Development Forum

ITCC European Consortium for Innovative Therapies for Children with cancer

SIOPE European Society of Paediatric Oncology

ENCCA European Network for Cancer research in Children and Adolescents

EMA European Medicines Agency

Mechanism of action biological process through which the medication causes the reduction in symptoms

Molecular targets molecules that cause the growth of cancer and are targeted by drugs

Paediatric The branch of medicine dealing with children and their diseases.

PIP Paediatric Investigation Plan

PMR Paediatric Medicines Regulation

Tumour a mass of cells growing in or on a part of the body where they should not, usually causing medical problems

Waiver a situation in which somebody gives up a legal right or claim

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