An opportunity not to be missed! Clinical Trial re-investment to build better research for better impact

Fox TA*, Horne GA*, Craddock C, Cook G, O'Brien S, Fox S, Hockaday A, Silk G, Hillmen P on behalf of the NCRI Haematological Oncology CSG.

*These authors contributed equally to this paper.

Clinical trials play a pivotal role in improving patient outcome in cancer and non-malignant disease[1,2]. Rapid assessment of novel therapies plays a central role in the evaluation of new drugs by National Institute for Clinical Excellence (NICE)[3]. In 2016-17, 670,000 people were recruited into more than 4,700 trials across the NHS[4] - consequent upon investment of more than £200 million annually into the Clinical Research Network of the National Institute for Health Research (NIHR)[5].

In the UK, cancer trials are developed by the National Cancer Research Institute (NCRI) and delivered by the NIHR. This internationally significant trial portfolio includes large phase III randomised controlled trials that usually compare the standard of care to new therapies and combinations[6]. The study drugs are often provided free-of-charge to the NHS by pharmaceutical companies. In addition to improving clinical outcomes by providing access to free drugs, accelerated trial delivery drives economic growth and represents a centrally important feature of the UK Life Sciences proposition, as articulated in HM Government's Life Sciences Industrial Strategy[7].

Blood cancer represents one of the most significant areas of recent therapeutic advance. Thousands of UK patients have benefited from access to often dramatically effective new therapies consequent upon clinical trial entry often before their routine commissioning by NHS England. In order to quantify this often-unrecognised benefit to the UK health economy we have calculated the direct drug savings from three of the largest clinical trials in common blood cancers; namely, chronic myeloid leukaemia (SPIRIT-2), chronic lymphocytic leukaemia (FLAIR) and multiple myeloma (Myeloma XII) (see Table 1). Non-trial drug costs were based on NHS England specialised commissioning pricing. Taken together these three trials provided access to more than £200 million free drug to 1737 trial patients. Consequently, in addition to the pivotal importance of these clinical trials in defining improved treatment strategies in three of the most important blood cancers they also generated substantial cost savings to NHS patients. These economies are amplified by the fact that in addition to receiving free drug the costs of standard treatment were not incurred by these patients either. Consequently, the cost savings across the whole NCRI trial portfolio is likely to be at least an order of magnitude higher than that outlined.

The savings identified in these three trials have been replicated in a range of early phase clinical trials in blood cancer delivered by the Trials Acceleration Programme (TAP), flagged as a beacon of best practice in the Life Sciences Industrial Strategy. TAP has produced more than £100 million of savings to the UK health economy whilst benefitting patients and fostering the pharma/NHS relationship. Such initiatives generate substantial value in the form of novel intellectual property and by acting as a magnet for inward investment into UK PLC.

The potential of the NHS to facilitate the acceleration of promising new agents from phase I/II trials to larger phase III trials through programmes such as TAP linked to NCRI Phase III Trials is huge. The NHS's unparalleled position to facilitate the transfer from early to late stage clinical trials within a single healthcare system should be embraced in order to rapidly accumulate evidence and improve outcomes for our patients. All UK patients, when feasible, should be offered the opportunity of entry into well designed cutting edge clinical trials.

Patient outcomes are currently being transformed by an unprecedented wave of novel therapies. The UK's inherent strengths in accelerated trial delivery is currently hampered by a number of bottlenecks including limitations in funding for clinical trial networks and protracted delays in trial set up. In order to continue to attract inward investment from the pharmaceutical sector and to enable the rapid assessment of novel therapies, consistent with HM Government's Life Sciences Industrial Strategy, a proportion of the substantial savings we have described should be invested into NIHR trials networks. Such investment is urgently required in order to deliver a clinical trials infrastructure which is fit for purpose in 2019 so that more patients can benefit from therapeutic breakthroughs as rapidly as possible and to release the enormous economic benefits of the UK life sciences sector.

Trial Name	SPIRIT 2	FLAIR	Myeloma XII
Disease	Chronic Myeloid Leukaemia	Chronic Lymphocytic Leukaemia	Multiple Myeloma
Number of Patients in Trial	812	1576	406
Number of patients Contributing to Cost Saving	406	925	406
How costs saved	1:1 randomisation between imatinib and dasatinib. Cost saving is because patients treated on dasatinib would otherwise have received commercial imatinib on NHS at full price. Saving accrued for up to 9 years as free supply of dasatinib was for 5 years from point of last patient recruited. Recruitment took 4 years.	Comparison of standard of care (fludarabine/cyclophosphamide/rituximab) vs Ibrutinib + Rituximab, Ibrutinib alone and Ibrutinib + venetoclax. Free IMPs in the trial were Ibrutinib (up to 6 years) and venetoclax (up to 6 years)	Non-randomised upfront treatment with ixazomib/thalidomide/dexamethasone. Standard of care is with bortezomib/cyclophosmamide/dexamethasone (6 cycles). Randomised to receive addition ixazomib with autoSCT and consolidation or maintenance.
Cost saving drug(s)	Imatinib	Fludarabine/cyclophosphamide/ibrutinib	Bortezomib/cyclophosphamide/dexamethasone
Cost-saving drug (inc VAT) per patient/year	£24,831	£14,814	£3,707
Total Treatment cost savings, based on cost modelling	£66,115,858/£75,238,584	£13,702,950	£1,505,212
'Free drug' saving, based on cost modelling	n/a	Ibrutinib: £202,926,276/£357,342,300 Venetoclax: £76,008,034/£120,047,274	Ixazomib: £25,038,858
Cost modelling	Patient years modelled on 100 patients accrued per year for 4 years, 406 patients on study for subsequent 5 years. Lower limit scenario assumes subsequent 10% annual dropout rate; upper limit assumes no drop outs.	Treatment cost saving is determined by patients randomised to an ibrutinib arm. Patient years modelling for 'free drug' (i.e. longer duration follow-up) assumes 6 year 'free drug', with upper limits assuming no dropout rate and no patients achieving MRD and lower limit assuming 10% annual dropout rate and a cumulative 30% achieving MRD negativity over the follow-up period (according to data from CLARITY).	Treatment cost saving is determined by patients randomised to ITD in induction. 'Free drug' determined by trial protocol (i.e. 6 cycles induction, 2 consolidation, and free maintenance for 25% of patients). Maintenance duration based on Tourmaline MM3 clinical trial time-to-progression (i.e. 15.2 months)

References

1 Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epi.* 2001; 54(3): 217-224.

2 Ozdemir BA, Karthikesalingham A, Sinha S, Poloniecki JD, Hinchliffe RJ, Thompson MM, Gower JD, Boaz A, Holt PJ. Research activity and the association with mortality. 2015 *PloS ONE* 10(2): e0118253. https://doi.org/10.1371/journal.pone.0118253.

3 Bell, J. Resuscitating clinical research in the United Kingdom *BMJ* 2003; 327 (7422): 1041-1043.

4 Boseley, S. Getting results: why NHS clinical trials are the envy of the world. The Guardian [newspaper online]. 2018 Jul 05 [cited 2019] Available from: https://www.theguardian.com/society/2018/jul/05/nhs-clinical-trials-other-countries-envious-getting-results

5 National Institute for Health Research. *NIHR Annual Report 2016/17. Improving the health and wealth of the nation through research.* 2016/17. Available from: https://www.nihr.ac.uk/about-us/documents/NIHR%20ANNUAL%20REPORT%201617%20FINAL.pdf [Accessed 10th Feb 2019].

6 National Cancer Research Institute. *NCRI Annual Review 2016/17*. 2016/17. Available from: https://www.ncri.org.uk/wp-content/uploads/2018/01/2017-Annual-Report-WEB.pdf [Accessed 10th Feb 2019].

7 Bell, J (ed), *Life Sciences Industrial Strategy. A report to the Government from the life sciences sector.* Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/650447/LifeSciencesIndustrialStrategy_acc2.pdf [Accesses 11th Feb 2019].