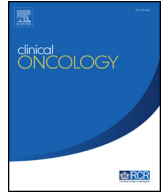




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## Editorial

## Marginal Gains and Clinical Trials – Improving and Influencing Practice

D.C. Gilbert<sup>\*</sup>, A.M. Henry<sup>†</sup>, A. Choudhury<sup>‡§</sup><sup>\*</sup> *Sussex Cancer Centre, Royal Sussex County Hospital, Brighton, UK*<sup>†</sup> *Leeds Institute of Medical Research, University of Leeds, Leeds, UK*<sup>‡</sup> *The Christie NHS Foundation Trust, Manchester, UK*<sup>§</sup> *Division of Cancer Sciences, University of Manchester, Manchester, UK*

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As the COVID-19 pandemic lingers on, clinical trials for patients with cancer have never been more important. Oncology is a highly evidence-based discipline, with much still to do, constantly striving to improve outcomes for our patients. The challenges COVID has wrought on already stretched health systems reduced enrolment of cancer patients into trials by over 60% [1]. Equally, COVID has demonstrated the advantages and opportunities for team science [2] and ambitious, multi-arm multi-staged trials through the success of RECOVERY [3], which itself borrowed many aspects from the ongoing MRC Clinical Trials Unit's STAMPEDE trial that sequentially changed the standard of care for patients with advanced prostate cancer over the last decade [4]. The requirements of healthcare systems to adapt quickly to a global pandemic have also accelerated acceptance of findings from oncology studies demonstrating equivalence of, for example, shorter fractionation schedules of breast radiotherapy [5]. Through initiatives such as COVID RT [6], changes in patterns of care can be assessed and pertinent lessons learned.

Although the results of the primary analysis are what drive changes in practice, clinical trials influence and improve patterns of care in more subtle ways. The rationale for the questions asked are instructive, and the trial management group will often have grappled with important decisions around how to define the control arm and standards of care. As such, clinical trial protocols are of significant interest over and above their primary question. This is of particular relevance in terms of, for example, radiotherapy studies where a clinical trial may first have to refine and detail current best-practice. This happened in the ongoing anal cancer platform PLATO [7], where intensity-modulated radiotherapy protocols were developed [8]

that then underpinned the dose escalation/de-escalation questions asked within the ACT4 and ACT5 components, respectively. The control arm of the trial thus influences departmental protocols for the treatment of 'off trial' patients. UK radiotherapy trials also have support from centrally co-ordinated Radiotherapy Trials Quality Assurance [9,10] for all relevant National Institute for Health and Care Research portfolio trials, again to give assurance around radiotherapy planning quality and delivery, which is of major benefit to departments and patients alike.

For these reasons, *Clinical Oncology* is launching a series of articles detailing current clinical trial protocols, starting with SCOPE 2 [11]. SCOPE 2 is a randomised phase II/III trial exploring the escalation of radiotherapy doses in patients with oesophageal cancer treated with definitive chemoradiation. An important additional component of the study is the investigation of adaptive therapy, in that it incorporates a phase II trial for patients with a poor early response using positron emission tomography/computed tomography. SCOPE 2 builds on the success of the SCOPE trial [12], which, although negative in terms of the primary outcome measures (testing the addition of cetuximab to chemoradiotherapy for oesophageal cancer), defined the standard of care regimen (two cycles of cisplatin and 5-fluorouracil) and radiotherapy volume definition and planning technique (50 Gy in 20 fractions, conformally planned) across the UK [13]. In terms of defining standard practice, SCOPE was accompanied by NeoSCOPE, assisting the re-introduction of neoadjuvant chemoradiotherapy in operable oesophageal cancer – again the associated radiotherapy quality assurance programme [14,15] was credited with adoption across UK centres and formed the basis of treatment protocols worldwide.

Alongside this initiative, *Clinical Oncology* welcomes either short overviews or full protocol papers of open trials or those in set-up informing colleagues of important current scientific questions, rationales and opportunities for

Author for correspondence: D.C. Gilbert, Sussex Cancer Centre, Royal Sussex County Hospital, Eastern Road, Brighton BN2 5BE, UK.

E-mail address: [duncan.gilbert2@nhs.net](mailto:duncan.gilbert2@nhs.net) (D.C. Gilbert).

improving patient care. We hope that the readership finds these articles interesting and useful and look forward to receiving submissions from a range of trial teams, where publication of the protocol will have significant benefits to the wider community.

## Conflicts of interest

The authors declare no conflicts of interest

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