The era of alternative designs to connect randomized clinical trials and real-world data

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In their Review published in the May 2019 issue of this journal (Real-world data: towards achieving the achievable in cancer care. *Nat. Rev. Clin. Oncol.* **16**, 312–325 (2019))[1], Booth et al. address challenges and future perspectives relating to the use of real-world data (RWD) in oncology. They describe the quality, and current and future applications of RWD, and the pitfalls of studies of comparative effectiveness using RWD. We acknowledge the authors' efforts to provide this comprehensive overview and appreciate the future perspectives they present. In light of the authors' appeal for increasing focus to be placed in the implementation of randomized clinical trials (RCTs) in real-world settings, herein we would like to address overlooked opportunities for using alternative trial designs to enhance the real-world nature of the data within RCTs. Owing to the length limitations of this Correspondence, we cannot define each modality but provide supporting references.

Pragmatic trial designs, such as registry-based RCTs (R-RCTs), have become of increasing interest globally as efficient and cost-effective tools that combine the advantages of a prospective RCT with the strengths of large-scale clinical registries. R-RCTs are characterized by low cost, enhanced generalizability of findings, rapid consecutive enrolment and the high potential for completeness in the follow-up management of participants, especially hard end points[2,3]. Although R-RCTs retain methodological limitations (for example, a dependence on the quality of the registry) and could face ethical challenges given the differences in national ethical guidelines[3], such studies can be designed to efficiently address research questions about comparative effectiveness in real-world settings.

The trials within cohorts (TwiCs) design, also referred to as cohort multiple RCT (cmRCT), is another innovative trial design of interest[4,5]. In oncology RCTs, this design enables the incorporation of methodological advantages, such as high recruitment rates, avoiding disappointment bias, improved generalizability of trial results and improved ethical acceptability when a two-stage informed consent procedure is applied[6]. The implementation of TwiCs in nationwide cohorts of patients with cancer brings researchers one step closer to achieving the achievable by using prospective RCT designs together with real-world follow-up data from cancer registries. Recently, several ongoing or completed TwiCs have been described[7–10]. Owing to the brevity of this correspondence piece, we highlight only the Prospective Dutch Colorectal Cancer (PLCRC) cohort, which serves as an infrastructure for a broad body of cancer registry-based research including (but not limited to) aetiological, biomarker, basic and (epi)genetic, interventional (TwiCs), and health-care policy and cost-effectiveness studies[11]. Additionally, tumour biospecimens and repeated population-based patient-reported outcomes (PROs) are collected within the PLCRC. PROs are enriched follow-up RWD available for TwiCs, as well as an important element that enables the implementation of learning health-care systems[12].

Future logistic developments (such as obtaining the patient's informed consent at hospital entry) will enable a closer integration of medical services into clinical research. Finally, innovations in clinical oncology practice by standardizing nation-wide entry of clinical data in electronic health records (EHRs) and subsequent implementation of electronic data-capture systems, which enable real-time data transfer from EHRs to national cancer registries, will support further improvements in quality and efficiency of RWD and cohort-embedded RCTs.

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Competing interests
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