Real World Data (RWD) is population or institution level data routinely collected either prospectively or retrospectively from non-randomised observational sources. Examples of these sources include electronic health records, billing claims, insurer databases, disease registries, treatment databases and national audits. RWD differs from data obtained from Randomised Controlled Trials due to the lack of external validity. In this edition of Clinical Oncology, Wadd et al. report treatment outcomes, using data collected for the Systemic Anti-Cancer Therapy (SACT) database from 3 NHS Trusts. For most agents studied marginally lower median survivals were seen when derived from RWD than median survivals in the published randomised controlled trials (RCT).For example median survival with the use of EGFR inhibitors in first line colorectal cancer (19months in the RWD cohort and 24months in the RCT) or Sorafenib in Hepatocellular Carcinoma (8.5months in RWD cohort versus 9.5-13.5months in RCT). Trifluridine/tipiracil had similar survival in the RWD to the associated RCT (6.7months in RWD cohort versus 7.3months in RCT).

There has been a surge of RWD publications in the last decade. A Pubmed search of "real world data" and "cancer" totalled 66 publications between 2010 and 2015, 817 between 2015 and 2020 and 1204 in the last two years. Before using RWD to inform cancer care we must understand when it does cut the mustard and when to take it with a pinch of salt.

To interrogate RWD quality Boyle et al performed a review of all RWD publications approved by the Food and Drug Administration and European Medicines Agency from 2010 to 2015 reporting the effectiveness of newly approved cancer therapies compared to the corresponding RCT. [1]. Of the 293 RWD publications identified only 2% were comparative cohort studies and 2% used national cancer registries. It is therefore not surprising that 78% were classified as low quality and 22% as moderate quality with no high-quality publications identified. The factors that were more likely to result in high quality RWD research included: the use of registry's to maximise sample size, funded research, the use of a methodological critical appraisal at publication to ensure transparency [2] and extensive methodological work to curate and develop specific indicators for missing, incomplete or incorrectly coded data.

How do we maximise the quality of a particular data source? Wadd et al chose to use the SACT database for their recent paper. The accuracy of the SACT database has been investigated by Boyle et al. who studied >10,000 Stage III colon cancer patients and reported 5,109 had a record of receiving adjuvant chemotherapy in the SACT database (84% of all those identified). However, with the addition of Hospital Episode Statistics (HES) a further 903 patients were identified demonstrating that use of

multiple data sources increases data quality and avoids under-capture [3]. Multiple data sources can also identify other data errors that occur in busy clinical settings. For example the inaccurate documentation of a performance status (PS) in an MDT where no one has met the patient can be picked up using a frailty score as a surrogate using HES coding generated by outpatient appointments and admissions. Another common real world error results when the clinician selects the incorrect reason for a treatment dose reduction from a drop-down menu, the correct reason can be identified using coding based on HES data which gives details on admissions such as procedure codes (eg. Colonoscopy) and diagnostic codes (eg. Colitis) [4].

In what circumstances is RWD used?

RCT funders like sexy, exciting, novel questions that recruit well, but not all questions fulfil these requirements. RWD can go some way to answering these questions but in order to do so robustly, there must be compensation for "bias in prescription" [5]. For example, to investigate whether time between short course radiotherapy (SCRT) and radical rectal surgery affects surgical morbidity, Levick et al. used the colorectal cancer data repository [6]. In this setting an example of "bias in prescription" would be clinicians allowing elderly or frail patients longer to recover from SCRT prior to surgery. This biases the result towards acceptable morbidity as fitter patients had surgery after a shorter interval than less fit patients but were likely to experience less morbidity due to their fitness, not necessarily due to the shorter time between radiotherapy and surgery.

RCTs are challenging to recruit in certain populations such as the elderly or in rare cancer groups. A Dutch group addressed optimal management of non-small cell lung cancer (NSCLC) in the elderly using a population-based time-trend analysis using the Amsterdam Cancer Registry [7]. Some funded RCTs fail to recruit, such STARS, ROSEL and SABRTooth trial in stereotactic body radiotherapy SABR versus surgery for NSCLC [8, 9]. RWD demonstrated equivalence and is delivered with confidence in patients wishing to avoid surgery [10, 11].

RWD can be used as a method of performance measurement to compare quality of cancer care across providers and stimulate quality improvement initiatives [12]. For example, investigating the 30-day mortality following systemic therapy [13] or identifying inequalities in access to curative cancer treatments such as lung cancer surgery or liver cancer surgery [14, 15]. Recently during the COVID pandemic RWD has proved to be invaluable in focussing minds on cancer services. It has highlighted the trend to delayed diagnosis and delivery of all treatment modalities in colorectal cancer also that

the number of radiotherapy fractions delivered particularly in prostate and breast cancer, fell as a result of the pandemic [16, 17].

RWD can contribute to implementation science, the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practise into routine practice [18]. RWD can investigate whether different providers have implemented results of RCTs into clinical practise. The IDEAL Collaboration confirmed that 3 months of adjuvant chemotherapy was equivalent to 6 months in colorectal cancer [19] and RWD has confirmed it has been adopted by UK clinicians [20], with real clinical and financial benefits.

There are instances where different trials have given different answers. RCTs of different fractionations in radical prostate radiotherapy concurred that cancer outcomes were equivalent, but with conflicting toxicity results. Using RWD from 12,133 patients comparable toxicity was demonstrated with RCTs comparing different fractionation schedules for prostate cancer [21]. Further research added the use of linked national Patient Reported Outcome Measures (PROMs) data to confirm minimal differences between the two approaches [22].

There are questions that can only be answered decades after trials have completed, well beyond toxicity data from a trial. For example the work by the Darby et al. investigating the correlation between an increased risk of cardio-pulmonary disease and breast radiotherapy has been performed with RWD from different sources. The initial publication used the US Surveillance Epidemiology and End Results (SEER) to investigate the rate of cardio-pulmonary related mortality in >300,000 woman and reported a correlation between mortality and radiotherapy delivered 10-20 years previously [23]. A follow up publication used the Swedish National Cancer Register and the Danish Breast Cancer Cooperative Group to confirm mortality correlates with mean heart dose [24]. This has led to a charge in heart sparing radiotherapy techniques now encouraged by national guidelines [25-27].

RWD provides an opportunity for understanding the economic costs and consequences of different options allowing robust cost analysis of illness in settings where in reality services and management will vary considerably across national populations [28]. This clearly helps to support Health Technology Assessment processes and reimbursement [29, 30].

Other RWD publications have been able to compare different technologies such as Intensity Modulated Radiotherapy (IMRT) vs 3D conformal radiotherapy where technology has been adopted without RCT evidence [31, 32]. Sujenthiran et al addressed the different toxicity with IMRT versus conformal radiotherapy in radical radiotherapy for prostate cancer and were able to avoid “bias in prescription” by comparing centres that had differentially adopted these modalities in the English NHS [31].

Finally, while RCTs remain the gold standard for answering questions around efficacy in our specialty [33] in the real-world we treat older, more comorbid patients, often those who would have been ineligible for the associated RCT [1, 34]. Therefore, it would be expected that outcomes or toxicity would be different in a real-world population. This is often termed the "efficacy to effectiveness gap" [35-37]. RWD can confirm or refute that a particular treatment has acceptable outcomes or toxicity in any given population, as XX et al have demonstrated in this edition of Clinical Oncology [38]. However, to take into account the "efficacy to effectiveness gap" there must be development of indicators that can pick up toxicities and longer-term outcomes in routine datasets. This will require considerable time for development so that they can be reliably used at scale to define new practices of care [39, 40]. Thus studies require robust research design, data quality and completion or comparative evaluation of populations, with collaboration with methodologists, to ensure appropriate statistical techniques.

What methods of RWD collection are available in the UK?

We have multiple tumour specific national audits for example in bowel, prostate and lung cancer [12, 41, 42] and national SACT and Radiotherapy Data Set (RTDS) databases collecting information on the use of our two primary oncological treatments allowing publications such as Hoskin et al [43]]. The Royal College of Radiologists (RCR) run very effective national audits that have gathered some of the largest cohorts of patients in rare tumour types and highlighted discrepancies of care [32, 44-46]. Examples of funded programs are the National Institute of Health Research (NIHR) Health Informatics Collaborative (HIC) collaborative, which gathers RWD from multicentre inhouse electronic systems [47] For example RAPID-RT is a funded project aiming to use real-world data to evaluate changes in practice and to optimise them in successive learning cycles [48]The ukCAT system builds on a European model where institutions create anonymised databases of routine data within their organisational firewalls which are made available to centrally distributed algorithms to learn from but critically at no point does any part of the source database leave the institution [49].

Lastly more recently there is interest in real world trials where RWD can be used to emulate target trials [50, 51]. Further work is required on all aspects of these trials before we are able to offer them as an alternative to RCTs.

In summary RWD clearly has an important role in research and development, particularly in settings where RCTs can not, have not, or will not provide an answer. But as with RCTs RWD needs to be well designed, appropriately resourced and use high quality structured data with integrated quality control. We must avoid the age-old discussion of RWD versus RCT's; they both offer unique and important data, each enhancing what we can learn from the other.

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