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Developing translational research infrastructure and capabilities associated with cancer clinical trials

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The integration of molecular information in clinical decision making is becoming a reality. These changes are shaping the way clinical research is conducted, and as reality sets in, the challenges in conducting, managing and organising multi-disciplinary research become apparent. Clinical trials provide a platform to conduct translational research (TR) within the context of high quality clinical data accrual. Integrating TR objectives in trials allows the execution of pivotal studies that provide clinical evidence for biomarker-driven treatment strategies, targeting early drug development trials to a homogeneous and well defined patient population, supports the development of companion diagnostics and provides an opportunity for deepening our understanding of cancer biology and mechanisms of drug action. To achieve these goals within a clinical trial, developing translational research infrastructure and capabilities (TRIC) plays a critical catalytic role for translating preclinical data into successful clinical research and development. TRIC represents a technical platform, dedicated resources and access to expertise promoting high quality standards, logistical and operational support and unified streamlined procedures under an appropriate governance framework. TRIC promotes integration of multiple disciplines including biobanking, laboratory analysis, molecular data, informatics, statistical analysis and dissemination of results which are all required for successful TR projects and scientific progress. Such a supporting infrastructure is absolutely essential in order to promote high quality robust research, avoid duplication and coordinate resources. Lack of such infrastructure, we would argue, is one reason for the limited effect of TR in clinical practice beyond clinical trials.

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Personalised medicine and the changing landscape of clinical cancer research

The integration of molecular data for supporting clinical decision making and improving patient management is now slowly becoming a reality (Ref. 1). Targeting the right drug to the right patient promises improved patient outcomes and helps avoid side-effects while reducing the overall healthcare costs owing to avoidance of unnecessary, toxic or ineffective treatment (Ref. 2). Pharmacodynamic read-out in patients during early phase clinical trials allows the potential for rational approaches to optimising schedule, drug combinations and dose for subsequent pivotal trials. Such translational research (TR) strategies will reduce the chances of missing effective treatment strategies for patients and can help in making early go/no-go decisions before commencing on costly late-stage trials, increasing the efficiency of drug development programmes.

To reach the goal of personalised medicine in healthcare, clinical research needs to adapt (Ref. 3). Clinical trials produce evidence-based medicines and TR within clinical trials produce evidence-based biomarkers relevant to everyday clinical decisions. Integrating TR objectives into trials allows the execution of pivotal studies that:

- are based on rational optimisation of treatment regimen based on biological endpoints;
- provide clinical evidence for biomarker-driven treatment strategies;
- allow targeting of early drug development trials to a homogeneous and well defined patient population, decreasing the likelihood of failure in clinical studies;
- support the development of companion diagnostics used to tailor treatments in the clinic;
- provide an opportunity to deepen our understanding of cancer biology and mechanisms of drug action;
- help understand unanticipated results of clinical studies.

Consequently, in cancer research, TR in clinical trials is beginning to change the clinical trial design paradigm and challenge the dogma of classical Phase I/II/III trials, with novel statistical design, window studies and maintenance therapy design of increasing importance for molecularly targeted agents. There is an increasing drive towards understanding the biology of disease and drug response at an early stage of the drug development process with early identification and integration of biomarkers into clinical trials (Refs 4,5). As a result, new types of study design are emerging that may be smaller in terms of the number of patients enroled, but which are heavily based on molecular biomarker assessments. Studies with adaptive designs are now emerging such as the BATTLE trial and I-SPY2, that allow the number of patients within specific molecular cohorts to be adjusted as information is gathered, allowing a focus on promising subpopulations enriched for particular biomarkers (Refs 6,7). Initiatives known as 'screening platforms' and other trial-related TR programmes are now emerging. For example, two initiatives in colorectal cancer include, the EORTC SPECTAcolor platform and the FOCUS 3 molecularly stratified, multi-arm randomised controlled trial (http://spectacolor.wordpress.com/, http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=6445). These screening platforms involve up-front assessment of a panel of biomarkers for every patient enroled. Biosamples arrive for central quality assurance and biomarker assessment from a variety of selected centres. Systematic analysis and documentation enables construction of a database of molecularly characterised patients which can be used to identify patients for enrolment into prospective clinical studies driven by the particular molecular sub-types of disease. The Cancer Research UK supported Stratified Medicine Programme in the UK is another example which aims to demonstrate the feasibility of routinely collecting biosamples from patients so as to construct a database of linked molecular data based specific genetic testing of the tumour which could assist in the design of subsequent cancer trials (Ref. 8). From the current trends it is apparent that access to samples, biomarker assessment and TR programmes now form an important and integral part of modern trial design and clinical research.

Challenges of TR and the need for a dedicated infrastructure

TR is multi-disciplinary and requires input and collaboration from many stakeholders in order to define the clinical need, deal with complex

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biology and interpret data while fulfilling study design and statistical considerations in a timely fashion. Consequently, the integration of molecular hypotheses, biosample collection and biomarker assessment adds challenges to traditional clinical trial development and leads to the necessity of establishing a supporting infrastructure and expertise. In this paper, we define the term comprehensive translational research infrastructure and capabilities (TRIC) which encompasses the technical platforms, dedicated resources and access to expertise managed in an organised quality assured way and governed in accordance with applicable legislation and good practice. TRIC associated with clinical trials plays a key role in supporting and promoting harmonised and high quality standards in research, from biobanking, laboratory analysis, molecular data collection, analysis and dissemination of results as well as providing infrastructure and logistical support and advice on tissue preparation/collection, informatics, statistics, legal and ethical frameworks to facilitate multi- or international institutional collaboration. Considerable resources are required, hence, TRIC is also required to provide support by providing access to highly-trained specialised staff, de-risking project set-up and facilitate the speed of study development with timely execution and dissemination of results.

Increasingly, the only way to proceed is by multi-institutional and international initiatives which require a culture shift towards coordinating, harmonising and ensuring value for participating centres. Clinical trial units and networks play an essential role in support of this work. Some examples include the EORTC headquarters (coordination centre) and the European based EORTC Network of Core Institutions (NOCI) network which promotes and supports high quality TR-driven clinical trials and cooperation between the EORTC Translational Research and Clinical Research Divisions and various EORTC Research Groups (Ref. 9). Also in the UK, the NIHR Cancer Research Network (NCRN) which is a network mapping directly onto the NHS cancer service networks across England with the NCRN Coordinating Centre managing the National Cancer Research Institute (NCRI) Clinical Studies Groups and working closely with NCRI-accredited Clinical Trials Units (www.ncri.org.uk).

The elements of TRIC

In developing TRIC associated with clinical trials, certain key elements must be established and integrated with the existing clinical trial infrastructures (Fig. 1). This includes biosample collection and biobanking resources, appropriate assay methods and laboratories to perform biomarker testing, supporting IT connectivity and data management for molecular data and biosample management, specialist biostatistics/bioinformatics expertise for molecular data analysis, publication and reporting. Developing standards, processes and minimum criteria for inclusion of TR into the trial protocol to facilitate this integration is a major role of TRIC. Other technologies such as imaging and virtual microscopy can also provide important TR components but are reviewed in detail elsewhere (Refs 10,11,12). A fundamental principle for integrating TR into trials is that the TR endpoints and objectives are clearly defined and minimum information such as assays and biosample collections, are specified in the trial protocol.

Access to biosamples

Access to the right type, amount and quality of biosamples for TR is fundamental to personalised cancer treatment, and one that is often a major bottleneck for clinical studies. Prospective collection of biosamples that are detailed within the study protocol becomes critical to support a new generation of clinical studies that are designed and driven by molecular hypotheses. Unique to clinical studies is the fact that access to biosamples may be absolutely required for patient enrolment since the molecular profile must be assessed as part of the objectives, this immediately sets more stringent requirements for access to and the quality of collected biosamples than in the case of correlative/discovery research (Ref. 13). In addition, it is increasingly appreciated that collection and storage of biosamples for future access provides an important opportunity for biomarker discovery and validation. Retrospective sub-group analysis is a valuable tool for defining distinct sub-groups of patients that show additional benefit from therapies, for example, demonstrating KRAS wild-type status predicting monoclonal antibody therapy response (Ref. 14). Therefore, adequate and quality assured biosample collection in clinical

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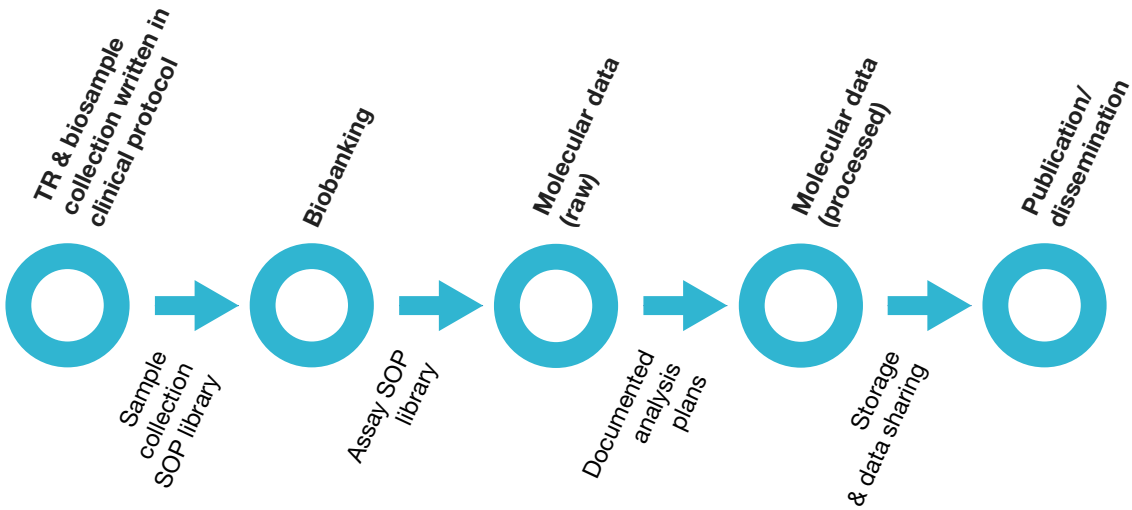

Figure 1. An illustration of the key elements required to establish translational research infrastructure and capabilities (TRIC) associated with clinical trials. Various processes conducted by various experts must come together in an integrated chain flowing from one process into another. In addition to traditional clinical trial platforms elements for biosamples management, access to laboratories for analysis of biosamples, collection, storage and analysis of translational research (TR) data and updating the publication and dissemination processes are required and should be performed under appropriate quality management systems with an audit trail.

trials is now becoming of paramount importance. To integrate biosample collection and biobanking into trials also requires additional consideration since a number of steps for collection, storage and processing must be integrated into the clinical trial operations and the use of the biosample within the clinical study must be taken into account.

A specific point to address for the collection of trial biosamples is that standard operating procedures (SOPs) detailing the specifications for biosample collection are particularly necessary in the case of multi-institute collections where variations in the method of collection or preservation could influence the molecular results and introduce biases or confounding in the final analysis. For biomarkers that are integral to the study design (e.g., stratification of patients or eligibility), the biomarker analysis method is known and hence biosamples should be collected according to evidence-based SOPs that are fit for purpose to ensure the biosample quality. For example, evidence suggests that delay in fixation of tissues has a significant effect on Ki67 assessment with the possibility for both false-negative and false-positive findings, and so tissue collection SOPs must be implemented according to the needs of the test (Ref. 15). For biobanking trial biosamples for future, as yet unknown research, then standard best practice guidelines for biosample collection can be adopted. Numerous international guidelines and best practices exist and are reviewed in (Ref. 16). At a minimum, a clear record of tracking the biosample from patient to fixation or freezer must be maintained. Biosample tracking and capture of biosample data through an appropriate biosample information management tool becomes paramount, not only to ensure an appropriate chain of custody but also for capturing key information on sample handling that may influence the final analysis that cannot be standardised via SOPs, e.g., such as some

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preanalytical procedures or deviations from SOPs like accidental thawing. Minimum datasets and standard coding systems can also assist greatly for the design of biosample data as well as for guidance on the final reporting of the biosamples used in analyses. Critically important for biosample collections as part of clinical trials is the link to the clinical database of follow-up data. This linkage can often be missing or incomplete in institutional collections of biosamples that are used in discovery research projects.

For tissues, the involvement of pathologists for assessing the tumour content, quality and other relevant pathological characteristics of incoming biosamples is critical (Ref. 17). A summary of useful tools and checklists that can assist in implementing biosample collections can be found in Box 1. All these tools serve to create a thorough, accurate and standardised collection of information regarding the nature and manner of handling of biosamples, as well as providing information on the collection of the biosample itself and remaining materials available with appropriate consent for future research. Notably, the entire process requires appropriate oversight and management in accordance with the prevailing regulations, current ethical principles such as appropriate consent and/or approval by an appropriate body, e.g., research ethics committee, as applicable. To facilitate this for multiple clinical trials, master contracts and agreements with participating sites can be extremely useful in facilitating the articulation of governance and regulatory regimes.

Biomarker analysis

In the new era of personalised medicine, biomarkers now play a variety of roles in clinical trials, ranging from patient inclusion (eligibility criteria), treatment selection, monitoring of treatment efficacy, toxicity and safety, mechanism of drug action studies as well as significantly contributing to the initiation and progression of new drug development and research projects. Biomarkers may be essential for trial design (e.g., integral), or the biomarker research may be a side-study and so is separate from the main trial design, e.g., correlative research, see Box 2 for examples (Ref. 29). Given the variety of roles a biomarker may take, it is important to consider in each case if the assay methodology is fit for the intended purpose and this includes the level of validation required for the role of the biomarker, the credentials and experience of the laboratory performing the analysis and the required documentation (Ref. 30). In addition, the EORTC is developing a checklist for laboratories that perform analysis of clinical trial samples to assist labs in ensuring that adequate measures are put in place; this also includes aspects relating to facilities and logistics since timelines for delivering assay results may be strict if patients are awaiting randomisation. For the addition of integral biomarkers in clinical trials, the investigators must carefully question the ultimate value of a biomarker in aiding clinical development or patient outcomes. For biomarkers that are an integral part of the trial design that have a direct effect on clinical decision making or patient

Box 1. Useful tools for establishing biobanking associated with clinical trials, with examples

- Standard operating procedures (SOPs) and guidelines for biosample collection (Refs 15,18)
- Minimum technical standards (Ref. 19)
- Biosample coding system including preanalytical variables (Ref. 20)
- Minimum dataset for biosamples (Ref. 21)
- Best practice guidelines for biobanking (Refs 16,22)
- Biosample information management tools (Refs 23,24,25,26).
- Operational checklist for integrating biosample collections in clinical trials (Ref. 27)
- Biosample reporting guidelines (Ref. 28)
- Quality assurance tools and certification programmes for biobanks
  - ISBER Self-Assessment Tool (SAT) for Repositories (http://www.isber.org/sat/)
  - EORTC quality assurance questionnaire for assessment of storage facilities
  - Confederation of Cancer Biobanks (http://www.ncri.org.uk/ccb/bestpractice.html)

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Box 2. Definitions of integral, integrated and correlative translational research (TR) studies: based on the National Cancer Institute (NCI) definitions

Integral studies – Tests that must be performed in order for the trial to proceed, that are essential for the trial design. E.g. 70 gene signature in MINDACT (Cardoso et al. 2007).

Integrated studies – Tests that are clearly identified as part of the clinical trial from the beginning and are intended to identify or validate assays, biomarkers or imaging tests that are planned for use in future trials.

Correlative studies – Tests being conducted in biosamples collected within a trial that is designed and powered to address another hypothesis, that are not integrated studies, e.g., MGMT methylation for correlation with patient outcome in archived biosamples from the EORTC 26981/22981, a randomised trial comparing radiotherapy alone with radiotherapy combined with concomitant and adjuvant treatment of glioblastoma patients with temozolomide (Hegi et al. 2005).

outcome (e.g., for stratification, eligibility, etc.) or that are included as primary or secondary research objectives of a trial then a high level of assay validation and good supporting data for clinical validity is required. Otherwise, biomarkers can be included as correlative studies or research endpoints as exploratory objectives and not require such detailed validation, but rather should conform to standard good scientific practice.

Prior to using trial biosamples, assays should be suitably analytically validated, i.e., the performance of the assay should be demonstrated and the assay is finalised and 'locked-down'. Various standards and organisations, for example, Good Clinical Laboratory Practice (GCLP) in the UK and the recent guidelines of the European Medicines Agency (EMA), recommend that laboratory work on trial biosamples can be conducted according to SOPs that have been tested and reviewed as being fit-for-purpose. Documents detailing validation data and experimental results should also be available along with a background or rationale, data and supporting publications showing the clinical validity and clinical utility of the test for the particular role in the trial (Ref. 29). Maintaining assay documentation ensures a traceable link between the collected biosamples and the data generated which can be invaluable when the resultant data are being analysed and interpreted.

The degree of oversight and stringency of validation and review of documentation must take into account both the nature of the technology and the role of the biomarker (Ref. 31). Similar approaches are being implemented by the EORTC and the National Cancer Institute of the USA (NCI).

Finding solutions to support researchers with the challenges of validating assay methodology for use as integral biomarkers in trials is challenging and various approaches are in operation. Several organisations have provided roadmaps or checklists to aid investigators with various aspects of biomarker research in trials. Cancer Research UK have developed roadmaps outlining the expectations for biomarker projects that are submitted for grant funding (Ref. 32) and the NCI have developed guidance and a study checklist for phase 2 and phase 3 trials that include biomarker assays or imaging tests (Refs 33, 34). Another approach is to provide supported access to appropriate analysis facilities composed of dedicated certified laboratories rather than providing grant funding for the work to be carried out locally, as is the approach of the Clinical Assay Development Program (CADP) of the NCI, USA. This approach provides an environment for appropriate development of fit for purpose tests and dedicated project management support to assist with coordination of development projects (Ref. 35).

Verifying quality and expertise, quality assurance and quality control

Quality assurance and quality control programmes (e.g., implementation of quality management systems, participation in ring tests, certification, etc.) become particularly important in the case of multi-institutional international clinical trials as has been demonstrated by observed variability in HER2 testing results (Refs 36,37). Access to facilities e.g., laboratories and biobanks, with appropriate expertise and experience becomes critical both for successful projects and for fulfilling regulatory obligations where applicable. For example, prevailing regulations in the USA

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require that integral biomarker tests that are reported to the clinician for use in clinical decision making must be performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory which guarantees a certain level of laboratory quality assurance and hence this applies to integral biomarkers in clinical trials whereas for correlative research, laboratories should instead be able to demonstrate that they have appropriate expertise to conduct the work (e.g., provide current curriculum vitae including publications). In Europe, the Clinical Trials Directive of 2001/20/EC provides provision for the inspection of laboratories that analyse or evaluate trial biosamples. Recently, the EMA released guidelines clarifying expectations for laboratories performing analysis of trial biosamples where the data will be used in dossiers submitted to EU/EEA regulatory authorities as part of a clinical trials application or marketing authorisation (Ref. 38). In addition to accreditation, internal and external quality control is also important. Internal controls such as the use of control biosamples and comparison of their values against control limits, should be an integral part of the assay testing procedure implemented locally. In external quality control programs the data of control biosamples are submitted to an external organisation for statistical evaluation, for example, UK NEQAS. This type of program serves to monitor long-term assay performance within a laboratory and allows investigators to interact freely within the network to discuss technical issues thus helping to improve the overall quality.

Although consensus on international technical standards and accreditation specific to biobanking is currently lacking, approaches for certifying or accrediting biobanks are ongoing. Examples include the ISBER Self-Assessment Tool (SAT) for Repositories (Ref. 22) and the EORTC quality assurance questionnaire for assessment of storage facilities. In addition, the NCRI together with the Confederation of Cancer Biobanks are developing a harmonisation and benchmarking scheme for biosamples used in cancer research (Ref. 39). These examples cover the general principles of quality management systems such as equipment qualification, validation of methods, resources, facilities, staff training, traceability, documentation, reference materials and participation in proficiency testing which form important aspects of high quality biobanking (Refs 40, 41). Other initiatives are taking a broader view, such as the Organisation of European Cancer Institute's accreditation programme for comprehensive cancer centres (CCC) that involves self-assessment and credentialing of a range of core competences, skills, resources and tools, including biobanking and laboratories, required for conducing high quality TR (Ref. 42).

Certification and accreditation of facilities becomes increasingly important to harmonise activities when work is conducted in a decentralised manner as it provides some confidence that the partners are working to similar standards. TRIC can support sourcing, accessing and coordinating this interaction through its central management, either via employment of trained experts or by sourcing external auditors.

Logistics and operational support

Conducting TR within the framework of clinical trials adds additional challenges to trial development and hence requires dedicated operational support. In developing clinical trial protocols tight deadlines and milestones need to be met and adding requirements for TR objectives must be done carefully in order to avoid a large effect on trial operations and timelines. Therefore, the integration of TR associated with clinical trials warrants careful upfront planning and streamlining in critical areas. To aid this process, the EORTC has devised a checklist for the integration of TR into clinical trials which can act as both an operational tool for internal management and as an educational tool for future investigators (Ref. 27). For integral biomarkers, the logistics and turn-around time for the biosample can be very challenging, particularly if the results are required for patient randomisation and/or treatment (Ref. 43). A recent example, testing and addressing the feasibility of these logistical challenges is the UK Stratified Medicines Programme which is focused on establishing the collection of biosamples to given standards, performing centralised testing and securing turn-around times in a clinically relevant timeframe coupled with collection of a minimum pathology dataset and centralised storage of data.

Data analysis

In the past decade, the field of TR has been plagued by poor study design leading to spurious

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conclusions or even directly contradictory results. Methodological issues stemming from small sample sizes and multiple hypothesis testing have resulted in a loss of power and inflated estimates of statistical significance of putative biomarkers (Ref. 44). In addition, the effect of technical variations and preanalytical variations on final test results and how they can lead to serious biases and obscure the effects and variation of interest is becoming increasingly appreciated (Ref. 45). These issues become particularly prominent for multiplex biomarkers, such as gene signatures, and when the TR forms an integral part of the clinical trial design e.g., affecting patient treatment decisions. Trained clinical trial statisticians must be involved early, not only in clinical study design for biomarker-driven trials, but also for correlative TR projects. A good example of an approach for providing access to appropriate expertise for development of projects is the network of 'Hubs for Trials Methodology Research' in the UK. Eight regional centres have been awarded funding for core staff and students who provide support and methodological input for UK trials research (www.methodologyhubs.mrc.ac.uk). Specifically, for clinico-genomics trials, it is now also recognised that in addition to (bio)statistical support, ensuring a good interaction with bioinformatics experts who have complementary expertise in the domain of complex classifiers is necessary. Recently, the NCI proposed criterion for –omics-based predictors used in clinical trials that reiterate the importance of rigour in TR data analysis. These criteria include verifying data accuracy and completeness, screening for artefacts in the data, evaluating the appropriateness of the (bio)statistical methods, locking down the algorithm, summarising the distribution of predictions and method validation including comparison against public sources of data (Ref. 46). Verification would also include logistics checks for data handling (such as data labels) and checking raw data formats, commented code and written descriptions of various analytical steps to document the statistics transformations being performed (Ref. 47). For these challenging –omics-based trials, introducing these key elements into the study development process and providing support for these through dedicated TRIC therefore becomes a necessity. Developing such trials with the support of TRIC provides the facility to link –omics data to documented potential confounding factors such as biosample collection SOP deviations, biomarker analysis SOPs including information on batch processing of biosamples and biological heterogeneity, information on tumour content and cellularity, that may prove to be critical in the final analysis and interpretation (Ref. 48) where a high level of evidence is required for the biomarker study, statistical analysis plans should be prespecified, available and documented (Ref. 49). Documentation and traceability can also facilitate exchange of code or scripts that serve to map the raw data to the final results. Many tools exist that can assist this process, such as literate programming tools such as Sweave, SASweave and odfWeave (Ref. 50).

Data management (clinical, molecular and biosample)

Clinical trials have a long tradition of data management. Validated data management systems are commonly available in trials organisations in order to ensure high quality data collection compliant with current data security and privacy standards (e.g., Good Clinical Data Management Practice (GCDMP) and 21 CFR Part 11, Electronic Records, Electronic Signatures FDA, 1997). Electronic data capture has grown considerably providing advantages for capturing uniform data from multi-centre studies, automated de-identification of data, study management and electronic data checks. Standard clinical information relating to the trial e.g., drug, dosage, eligibility criteria and clinical outcome and so on, are therefore, often well managed within standard clinical trials databases. However, including the TR objectives in trials poses additional challenges which will probably require the standard IT platform to be extended with additional functionality. This includes provisions for workflows for biosamples, molecular data and administrative or even cost data (Fig. 2).

Integrated IT platforms

Interoperable databases and supporting IT solutions are a foundational building block of TRIC. With the rapidly advancing capacity to quickly generate large volumes of molecular data, IT platforms for organising, storing and linking data in a robust and secure way become critical. One of the major challenges of building

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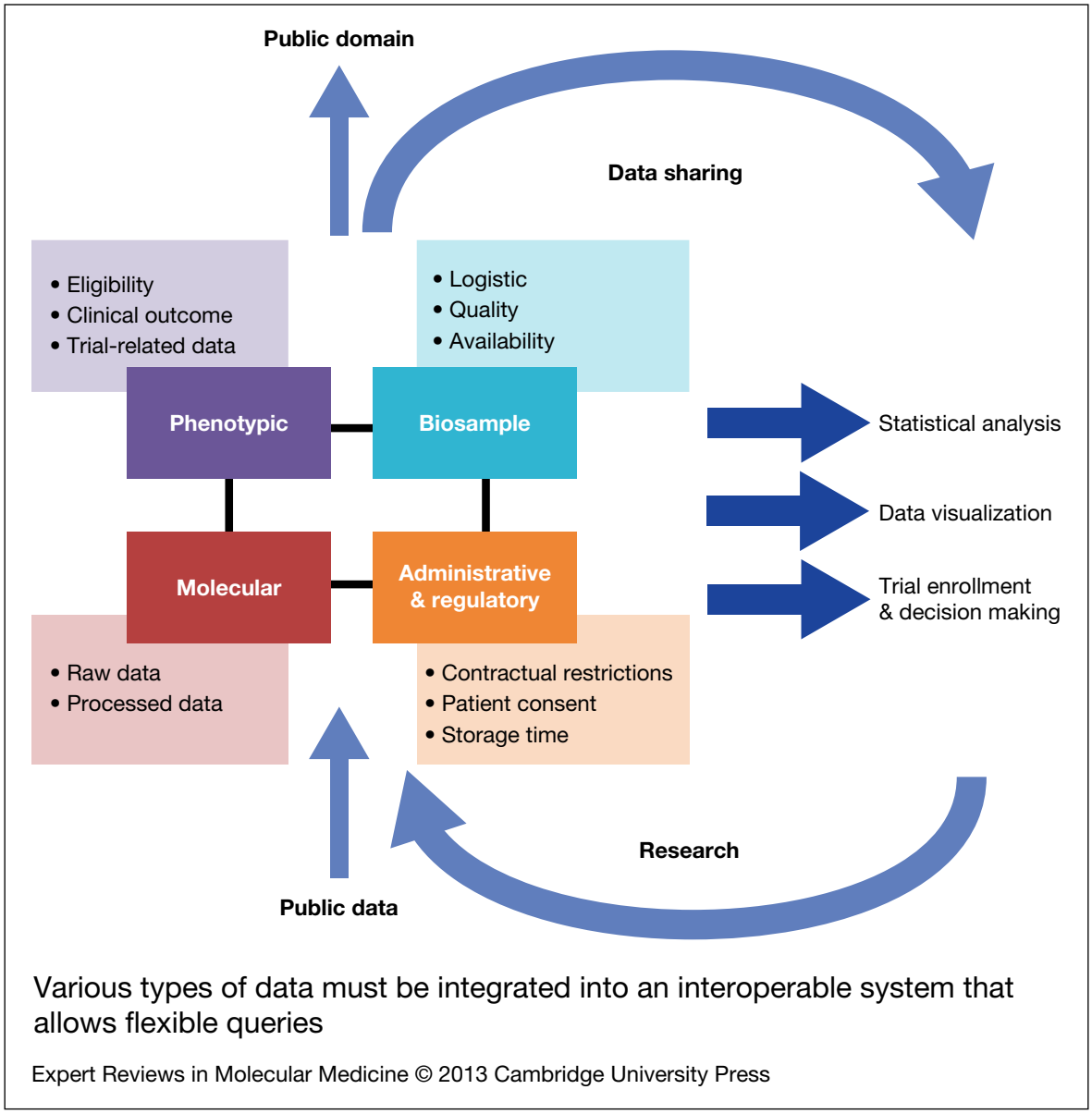

Figure 2. Various types of data must be integrated into an interoperable system that allows flexible queries. Examples of each data type are provided. Capturing and integrating the data in a modular way allows flexibility in search functions and data retrieval in a format that matches the needs of various user groups. The integrated database provides a resource for future research which may involve external data, this can in turn feed more information and knowledge back into the system. Data may be downloaded or shared in collaborations or placed in the public domain, as appropriate.

IT solutions for TRIC is the diversity of the data and formats to be collated, particularly if the data are sourced from different institutions or partners. Data can range from large volumes of molecular results to clinical outcome or even administrative information. Increasingly, projects require the ability to link between datasets or operations to allow cross-database searching, for example, combining molecular and clinical information to identify patient groups with biosamples suitable for future research studies or even combining scientific with financial data for cost effectiveness research. Appropriate IT tools can also help support compliance with governance and regulatory checkpoints, e.g., project milestones, billing and regulatory

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restrictions, scope of patient consent for future research studies, data access rights, institutional contact details, custodianship and contractual restrictions. Whether the selected solution is a one-stop-shop platform or involves combining a series of different softwares, given the diversity of cross-database queries, interoperability between systems is the main goal. Functions for workflow management and repeatable automated report generation that build and record the sequence of steps become important for traceability and integration.

As part of developing such IT platforms, formalised data structures, ontologies and common data elements/minimum datasets, become critical for efficient linkage, retrieval, interpretation and exchange of data, particularly for international or multi-site studies (Ref. 51). Using common data standards saves time and resources and lends itself to automation and interoperability of systems. It also increases the quality of the data and the ability to re-use data for secondary research projects by facilitating data exchange and communication between partners. Several international initiatives for inter-institutional harmonisation are currently underway such as Clinical Data Interchange Standards Consortium (CDISC) (www.cdisc.org) and Critical Path Institute (C-Path) (http://c-path.org).

To successfully incorporate TRIC with traditional clinical trial databases, additional IT modules for biosamples and molecular data are needed. Consistently recording and tracing biosamples through multi-stage analytical processes is critical for maintaining the audit trial of biosamples and for future usage of the biobanking resource. Biosample metadata, including both logistical information (type of biosample, location, shipment batch number, remaining tissue available etc.) and quality parameters (e.g., time until freezing, fixation method, tube type for blood collection, etc.) are needed. Making provision for biosample data management is a large task that should not be underestimated. Many organisations are developing tools for this purpose, including the NCBI (Ref. 23), the European Bioinformatics Institute (Ref. 24), IARC (Ref. 25) and caTissue (Ref. 26).

Another key additional IT module for TRIC is that linking molecular data to clinical trials. Different approaches to this task can be implemented. One is to centralise data for management by TRIC, however, this requires securing adequate storage space, tools and expertise to enable management or large volumes and diverse types of biological data. The resources required can be particularly significant in the case of new technologies such as next generation sequencing (Ref. 52). An alternative is the federated model where links to specific storage locations are established, e.g., partner institutes or public data repositories. Existing specialised data repositories (independent of clinical trial infrastructures), such as the European Genome-phenome Archive, may be well positioned to provide these specialised services. Notably, greater accessibility, awareness and harmonisation between available bioinformatics resources has been identified as a key area for further development within Europe, as exemplified by the opening of ELIXIR, a pan-European bioinformatics infrastructure for biological data (www.elixir-europe.org).

Finally, the collected data must be interpreted in order to gain knowledge, therefore, analysis and visualisation tools become important to support the generation of new knowledge and complex decision making (Ref. 53). These tools may be either integrated into the IT platform or may be separate stand-alone softwares. Since numerous analysis softwares (both open source and propriety) are available to researchers, data should be accessible for downstream use in a way that allows researchers the freedom to select the analysis tool of choice (Ref. 54). Critically, whatever IT solution is adopted for TRIC, it must have a user-friendly interface in order to be adopted.

Challenges

As efforts in building TR platforms proceed, it becomes apparent that several key challenges still need to be addressed.

Governance

To ensure appropriate governance and management, the roles and responsibilities of the stakeholders must be defined through a transparent governance structure and internal procedures. This allows smooth operation of the TRIC and inter-institutional cooperation while complying with appropriate legislation. Policies are necessary to establish the ground rules of

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operation. The challenge, however, is to maintain streamlined processes that are simple and feasible to implement. Quality control, risk management and monitoring plans should also be built into managerial oversight. Ethical review and oversight of research including patient consent and ethics review according to the applicable laws are needed as well as review by independent scientists, statisticians and patient representatives must be carefully considered. Mechanisms for timely interaction with key regulatory bodies such as research ethics committees or specific regulatory bodies (as applicable) become critical for timely initiation of projects.

A variety of governance models can be observed in different organisations. For example, many discussions have centred on the question of custodianship of biosamples (Ref. 55). In some models, the custodian may be linked to the physical location of biosamples (e.g., confederation of cancer biobanks), may be designated to a legal entity e.g., institution or hospital (MRC) or with individual responsible persons (GSK) or may be defined as the body deciding on the use of the biosamples (e.g., the individual contributing institutes of the EORTC). Particularly in the case of clinical trials, the roles, relationship and responsibilities of the custodian and trial sponsor must be clarified as these may vary between organisations and should be agreed upon when collaborations are initiated.

Regulatory

Several challenges in the area of regulatory compliance will almost certainly arise during the development of TRIC. Principally, accessing and exchanging stored biosamples for new research projects is a critical yet still challenging task in the case of multi-institutional or international collaboration. In the EU currently, there is no single overarching binding legal instrument regulating the use of biosamples but instead a patchwork of national member state regulations exists (Ref. 56). A lack of mutual recognition of decisions leads to multiple country-specific submissions and approvals and sometimes even contradictory recommendations of oversight bodies (Ref. 57). This can add hurdle, increase administration and costs and could affect the feasibility of conducting projects.

Similarly, challenges also arise in data sharing. As the goal is to stimulate research and expedite transfer of knowledge to the clinic, it is important that research results and associated data are made available in the public domain for use by the larger scientific community in an appropriate manner. However, various factors must be balanced in order not to undermine the interests of stakeholders that could dis-incentivise participation. For example, in clinical trials, constraints may exist regarding the timing of publication of TR results relating to trial endpoints and there may be restrictions on the scope of data that can be released in the context of clinical trials e.g., ensuring that the released clinical data are mature, datasets are thoroughly cleaned and that the release of TR information does not prematurely reveal trial results. Commercial interests may also be represented and the needs for securing competitive positions and intellectual property rights must be taken into account.

Data exchange and storage processes must also comply with the prevailing regulations on privacy, confidentiality and security regarding personal and sensitive data. This is leading to heated debates in some areas such as publicly releasing genome sequencing data which can be used to identify individual participants and which may reveal sensitive health information about individuals (Ref. 58). Medical data are considered sensitive information and debates still continue regarding appropriate models for accessing medical data for research, for example, whether patients should be re-consented for secondary use of data in research. Additional regulatory challenges may arise when exchanging data and biosamples outside Europe, especially to the USA, because of differences in data protection laws. Novel methods in computing and IT could help overcome some of the international regulatory restrictions for data sharing, for example, the project DataShield exemplifies an approach that allows parallel access to and analysis of data that are physically distributed in various locations (Ref. 59).

In any case, it becomes clear that current approaches need to be updated in order to deal with international collaborations involving many researchers and the possibility of secondary use of biosamples and data. New, innovative ways of approaching multiple stakeholder interaction through the use of information technology applied to governance (e-governance) are needed (Ref. 60). This principle is exemplified by the

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ENCORE project which allows consent to be collected from participants through an ongoing basis, allowing the patient better control and input into secondary uses of biosamples and data and provides a means for the patient to withdraw consent (www.encore-project.info/index.html). Once approved, institutes participating in these types of approaches could be granted exemptions from a full ethical review, helping to expedite research.

Access to expertise and culture change

Medical care is becoming increasingly interdisciplinary. When conducting TR in clinical trials we can now expect the contributions of surgeons, pathologists, molecular biologists, biobankers, statisticians, bioinformaticians, imaging experts etc. in addition to clinical expertise. Therefore, an essential element and added value of the TRIC is to coordinate and provide access to the required expertise at appropriate time points during study development. In many cases, the interaction of disciplines must be supported at a very early stage at the concept development. Several organisations have opted for review committees composed of multiple experts to support and verify the TR projects associated with trials at critical time points during development (e.g., NCRI Biomarkers and Imaging Clinical Studies Group and the EORTC Translational Research Advisory Committee). For this scenario, the timing of the constructive input and additional work required to optimise the TR project become critical factors for successful coordination. Other approaches involve connecting experts directly via expert networks and facilitated networking platforms that help investigators in searching for potential collaborators and find related resources across institutions such as the DIRECT2Experts network (Ref. 61). A third example is the use of a 'knowledgebase' that collates available guidance and expertise e.g., statistics training, online journal club, educational materials, templates and standards, into a single portal for easy access such as CTSpedia (www.ctspedia.org).

Funding

One of the current major barriers that will probably continue to persist in the years to come is securing adequate funding to establish and maintain the TRIC. The initial start-up investment required for establishing the TRIC is substantial, even just for the biobanking aspect alone. However, particularly pertinent is the lack of long term and sustainable funding needed to maintain the TRIC e.g., ensuring adequate coverage of staff salaries, daily running and operation costs needed to ensure smooth functioning (Ref. 62). TRIC requires access to specialised expertise, both for operational/quality assurance and scientific expertise. Different mechanisms have evolved for supporting this. In the UK, one approach to address this has been through the Experimental Cancer Medicine Centre (ECMC) Network (www.ecmcnetwork.org.uk) where dedicated centres receive funding from the Department of Health together with Cancer Research UK. This provides a long term resource and access to experienced staff to support quality assurance for biomarker development and early phase clinical trials as part of a dedicated infrastructure underpinning early phase clinical trials, biomarker research and biobanking activities. Also, CRUK and the Medical Research Council support clinical trials units (www.ukcrc-ctu.org.uk), which provides support from trial concept to implementation. In the USA, for successful applicants, the NCI CADP program supports access to the institute's assay development and validation resources which also includes specialised laboratory and scientific staff and project managers for operational support. This demonstrates that the funders may be open to supporting specialised staff within key infrastructures who can work together with the applicants to develop trial concepts and application for new therapies, as well as advising on quality matters. However, decision making committees that approve protocols for scientific rigour may be less likely to receive funding support owing to reasons of maintaining their independence, although in some cases a nominal honorarium may be offered.

In addition to funding the challenges of the TRIC, the economic downturn has affected pharmaceutical companies, private foundations, universities and other nonprofit organisations, and has led to reduced research and development budgets. With the increasing costs of clinical research, the additional collection and long-term storage of biosamples for future, as yet unknown research projects, can be difficult to justify. Grants for specific TR projects may be available for a variety of sources but often these

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are project specific or may follow project-specific renewals. Cost recovery mechanisms that charge the end user for services and resources used are increasingly implemented in an effort to maintain sustainability; however, these may be difficult to implement with the blessing of all the stakeholders.

Outlook/future directions

Harmonisation

The challenges in designing and successfully executing TR are significant and the field must gain sufficient critical mass to be able to overcome them. International harmonisation and coordination are essential for enabling exchange of information, collaboration and accelerating scientific advances. For example, in Europe, the clinical trials directive is being revised and aims to implement a central portal for coordinated submission of European clinical trial protocols. Similar regulatory harmonisation covering research on biosamples is currently lacking (Ref. 63). In the area of TR, an ambitious programme called the EurocanPlatform aims to create a European infrastructure for translational cancer research and includes modules for early and late TR, including clinical studies. In addition, the European Strategy Forum on Research Infrastructures (ESFRI) roadmap includes European infrastructures for pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), and ELIXIR for biological data. These initiatives play a key role in disseminating standards and promoting efficient cooperation and must coordinate between disciplines enabling interoperability between data and services in the biological, medical, translational and clinical domains. International cooperation is also needed, particularly for supporting research in rare cancers. One example of an international effort is the WIN consortium biomarker database registry that aims to catalogue biomarker studies being conducted within the framework of clinical trials (Ref. 64). The goal is to consolidate the field of biomarker research to help avoid redundancies and accelerate adoption of promising candidate biomarkers. Harmonisation, collaboration and networking are therefore needed in order to allow efficient organisation, facilitate financial stability and to enable more rapid progress in research.

Stakeholder involvement

TR involves a number of different stakeholders. For example, clinicians, scientists, surgeons, pathologists, molecular biologists, bioinformatics and statisticians are all required to produce a successful TR project. These different disciplines need to be represented and involved within the TRIC. In particular, patients are playing an increasingly active role in clinical research and can be a significant driving force in supporting new ways to overcome the challenges in building and maintaining TRIC. For example, with increasing use of the internet, many people are sharing information much more easily and willingly than in the past as demonstrated by the website PatientsLikeMe (Ref. 65). This means that individuals could begin to set the level of privacy that they wish to have regarding their own data. Patients can also contribute by providing additional previously uncaptured data by directly reporting their experiences in real time (Ref. 66) and can also be involved in review processes such as writing patient information and consent documents and participating in ethics committees and tumour boards where research projects are approved. More importantly, patients have a voice that can help in lobbying for streamlined harmonised regulations helping to lift unnecessary regulatory burdens that can hinder scientific progress, as well as supporting fund raising for research and highlight research questions that are directly relevant to patients.

New models of partnership

TRIC associated with clinical trials creates value that can help catalyse cancer research. TRIC supports harmonising processes, adoption of best practices, improved clinical decision making, less costly clinical studies, development and optimisation of information technology, data generation, access to expertise and hence innovation in science. Hence, TRIC creates value that can be of interest to a range of stakeholders including patients, governments, pharmaceutical and diagnostics companies as well as academic researchers and opportunities arise for collaborations and synergies. New models of partnership are surfacing promoting precompetitive collaborations between companies that offer sharing of selected data and joint troubleshooting of fundamental issues

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that offer no competitive advantage to any one firm e.g., building common standards. Sharing of program resources and pooling capabilities can increase the effectiveness of research for understanding complex disease networks and improve economies of scale which can help reduce costs (Ref. 67). This can foster public-private partnerships and avoid potential barriers that can arise as a result of claiming intellectual property (Ref. 68). This principle is exemplified by a joint undertaking between the European Union and the pharmaceutical industry association (EFPIA), called the Innovative Medicine Initiative (IMI). IMI is Europe's largest public-private partnership aiming to streamline and innovate in drug development and is supported by a €2 billion euro budget for collaborative research projects (http://www.imi.europa.eu/). It is hoped that through these new models of partnership, many of the key challenges facing the development of TRIC can be overcome.

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Features associated with this article

Figures

Figure 1. An illustration of the key elements required to establish translational research infrastructure and capabilities (TRIC) associated with clinical trials.

Figure 2. Various types of data must be integrated into an interoperable system that allows flexible queries.

Boxes

Box 1. Useful tools for establishing biobanking associated with clinical trials, with examples.

Box 2. Definitions of integral, integrated and correlative translational research (TR) studies: based on the National Cancer Institute (NCI) definitions.

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