NCRI
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Institute

In partnership with

Royal College of Surgeons
ADVANCING SURGICAL CARE

Future of Surgery

Report of the NCRI Series of five Workshops

Partners in cancer research

NCRI Partners

NCRI is a UK-wide partnership between research funders working together to maximise the value and benefits of cancer research for the benefit of patients and the public. A key strength of the NCRI is our broad membership with representation across both charity and government funders as well as across all four nations in the United Kingdom.

Executive Summary

We have entered a 'golden era' for medical oncology, with a vast array of novel systemic therapies available, and already step changes are being made in the outcomes for patients with advanced cancer. Conversely, although there are pockets of excellence, academic surgery is in decline and there is a need for focus on the critical research contribution made to cancer care by surgical oncologists.

Firstly, NHS surgical oncologists who are essential to the successful delivery of surgical trials, are increasingly stretched and research is not always prioritised. Secondly, following a reduction in training time in surgery (and often to the consequent exclusion of formal research) clinical research fails to be embedded in training and therefore the culture of surgical oncology. Thirdly, the unique working environment and patient presentation within surgery make introduction of clinical trials challenging. In view of these and other issues, a surgical oncology initiative was developed by the NCRI in 2015 resulting from a key report reflecting these issues in 2012. The initiative, which was also co-funded by Royal College of Surgeons of England, constituted a series of five workshops in 2016 and 2017 around the specific nature of surgical trials in order to inform, deconvolute and plan for the future.

The Future of Surgery workshop series led by the NCRI has identified important gaps in clinical knowledge and given direction to themes for further clinical trials. Additional findings include:

- There is a need to consider alternative methodologies such as cohorts and registries to collect important data in rare diseases, emergency presentations, frail or elderly patients and such previously un-researched but important areas of oncology where surgeons contribute
- By working closely with the surgical research community, trial funding bodies can support and nurture surgical research in the UK in the context of surgery being a complex intervention with differences in phases of researching new operations and devices
- New opportunities for effective cancer surgery have arisen from the promising outcome of effective systemic therapies and minimally invasive surgery, all requiring novel approaches to generating reliable evidence, some of which may span several tumour types and anatomical sites

We feel that this globally unique series has yielded important guidance and a direction of travel for the surgical oncology community to learn from.

Yours sincerely,

Professor Richard Shaw, on behalf of all co-authors (see Appendix one for full list).

Introduction

The National Cancer Research Institute (NCRI) was set up as a key recommendation of the NHS Cancer Plan in 2000[1], to facilitate a decentralized model of cancer research in the UK, and act as a hub between government, the voluntary and private sectors. As a UK-wide partnership of cancer research funders, NCRI is well placed to identify where collaboration adds value. Through partnership working it can capitalise on opportunities, address challenges and strengthen existing work to improve the outcomes of cancer patients. In 2012, the NCRI published a report titled "Challenges and opportunities in surgical cancer research in the UK"[2]. The report highlighted the prominent role of surgery in cancer care; achieving half of all long-term cures and providing the cornerstone for treatment of most solid malignancies. The report also highlighted a specific paucity of research in the field of cancer surgery. It recommended that steps be taken to accelerate the development of surgical cancer research and support the sharing of research skills amongst surgeons using existing structures.

From the perspective of clinical trials, or at least prospective protocol-driven research, surgery has developed from a low base, infamously described in Richard Horton's Lancet editorial "Surgical research or comic opera"[3]. Initiatives by the National Institute of Heath[4] and Royal College of Surgeons of England[5], as well as the NCRI have helped to drive improvements in the surgical trial portfolio. For example 8774 patients were recruited to surgical oncology trials during 2015/16 rising to 11910 during 2016/7; this represents approximately 15% of all activity in the oncology portfolio for both years[6]. However, recent growth in surgical research has not been uniform. Marked discrepancies are observed in research opportunities offered to patients between the surgical specialties.

For surgical research to be adopted more widely, several challenges must first be met. Methodologically key issues of standardisation and quality assurance must be addressed as they relate to the delivery and evaluation of these often complex interventions as highlighted [7]. As a profession, reflection about the nature of surgery must occur. Is it a science or a 'craft'? While surgeons undoubtedly make a substantial investment in the acquisition of skills and techniques this should not be allowed to bias individual equipoise.

In response to these challenges, and to meet the recommendations of the 2012 NCRI report, an advisory group was convened, comprising a surgical representative from each of the site-specific NCRI Clinical Studies Groups. The role of this group was to prioritize themes for a series of five workshops with an overarching title "Future of Surgery". Five workshop themes explored methodologies that underpinned conduct of surgical oncology studies (Table 1). These themes represented trial paradigms and challenges unique to surgery. Each workshop developed a cross-cutting agenda that aimed to share existing skills and experience, but also identify gaps in knowledge. The workshops brought together key stakeholders including patients, publishers, charities, funders, and clinicians (including surgical trainees) and were conducted over 2016/17. This paper highlights the methodological challenges and priorities for research in surgical oncology that arose from these workshops.

Table 1: Future of Surgery Workshops

1. "Trials are only as credible as their endpoints": Defining the future outcomes of surgical research
2. "Technology trials in surgical oncology": What evidence is required prior to introduction of new technologies into surgical practice?
3. "Selecting patients for surgery": Decision making, informed choice, fitness and frailty stratification and measurement.
4. "Extent of surgery and peri-surgical 'window-of-opportunity' trials"
5. "Surgery for metastatic disease"

Trials are only as credible as their endpoints

Failure to select, measure and report appropriate outcomes can have a major deleterious effect on the impact of clinical trials, waste research resources and delay the implementation of novel therapies[8]. Selecting meaningful and measurable outcomes is particularly challenging because of the complexity of surgical interventions. Five key challenges in surgical outcomes methodology have been identified:

Define quality assurance outcomes in surgical trials

Quality assurance is a major barrier to successful surgical trials. Surgery is complex, and it is critical to consider the degree of surgical standardisation and the impact this has on overall study design[9]. Trials that allow the flexible delivery of surgical interventions (i.e. pragmatic trials) aim to provide "real world" evidence that is relevant to clinical and policy decision makers. For example, the recent EthoS[10], ROLARR[11] and STAR_TREC[12] trials compare standard and novel surgical treatments with little restriction on how the treatments are delivered. Pragmatic designs, however, may fail to detect important differences in treatment efficacy precisely because of variation in surgical technique. Surgical quality assurance outcome frameworks[13] recommend deconstructing surgical interventions into their constituent components and setting out mandatory, optional and prohibited steps *a priori* for monitoring. Further work is now needed to implement these recommendations into specific clinical areas.

Define process outcomes in early phase surgical studies

Early phase surgical studies involve the iterative development of interventions in preparation for further evaluation[14]. Surgeons, for example, may modify and optimise new techniques as they become more proficient, or devices may be redesigned in response to *in vivo* studies. There are currently no recommended outcomes for this process or guidelines on how to determine when this iterative development phase is complete.

Further the development of core outcome sets in cancer surgery including recommended measurement instruments

Core outcome sets (COSs) are a standard set of outcomes, agreed by patients and researchers, to measure in all trials in a clinical area to facilitate evidence synthesis and reduce outcome reporting bias[15]. The benefits of COSs have been widely recognised and their use recommended by research funders, regulatory bodies and journal editors. Several surgical COSs exist in surgery including breast reconstruction[16], colorectal cancer[17] and bariatric surgery[18], however, some are deficient in many clinical areas. Furthermore, there are a lack of recommended instruments to measure COSs, and few COSs that define safety and efficacy outcomes in early phase surgical studies.

Outcome selection in pilot/feasibility studies

Feasibility studies are those that assess whether a future study can be done[19]. Pilot studies can be considered a subset of feasibility studies that are a miniature version of a main trial that tests components such as recruitment, equipoise, randomisation and follow up assessments. Pilot study data may contribute to the main trial (internal pilot) or analysed separately (external pilot). The complexity of surgical studies often mandates detailed pilot/feasibility testing prior to full randomised evaluation. This is an opportunity to assess the validity and acceptability of potential outcomes in target populations, model the optimum timing of assessments, identify the most clinically meaningful primary outcome and measure process outcomes including recruitment rates.

Methods to maximize consumer involvement in outcome selection and measurement

Consumer involvement (patient and public involvement (PPI)) is important in the selection and measurement of surgical trial outcomes. In the face of different types of outcomes including clinical, patient reported, composite (such as combining stroke, myocardial infarction and cardiovascular death into “major cardiovascular event”)) and surrogate (such as cancer recurrence substituting for cancer survival), further research is necessary to optimise patient involvement in outcome selection.

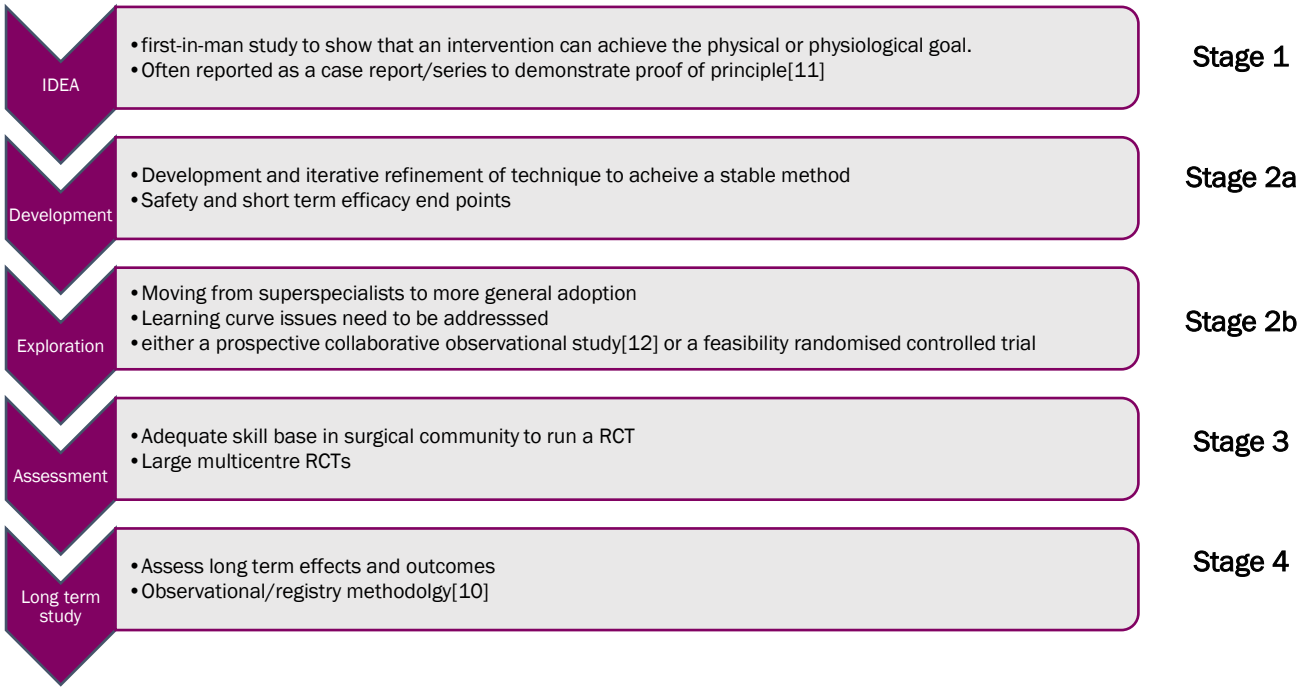
Knowledge gaps and recommendations

- Further methodological work into a surgical quality assurance outcome framework.
- Expansion of core outcome datasets into a wider range of diseases and sites.
- Develop and standardise primary outcome measures in pilot and feasibility phases of surgical trials, including the contribution of consumer involvement in the choice of outcome measures.

Technology trials in surgical oncology

Surgical procedures are generally complex interventions where outcomes are dependent on the operator, team and their setting. Surgery is very dependent on technology – innovation comprises new techniques, modified strategies or development of new surgical technologies. Unlike new drugs there is neither a clear evaluation pathway nor a regulatory framework that requires proper evaluation before introduction[20]. As a result, many surgical technologies are introduced without evidence and, in some cases, are only shown to be ineffective or even harmful after it has been used in many patients (e.g. metal-on-metal joint replacements [21] or PIP breast implants). The IDEAL collaboration was set up in response to this problem. Their framework provides a method of surgical innovation that follows a distinct pathway different to drug development pathways [9]. This pathway consisted of five stages (Figure 1) each with a specific goal and recommendations.

Figure 1: IDEAL Framework



We need to work with funders so that they can better understand the funding requirements needed to support IDEAL studies and it may be that discrete funding arrangements will need to be developed to promote good quality technology trials.

The introduction of new medical/surgical devices has its own set of regulations that leads to CE marking. Award of this means the device complies with essential requirements of the European Product Directives i.e. the device does what it is supposed to do but provides no data on the efficacy, safety or comparative efficacy of its use in clinical practice. The difficulty is that this technology can be used in patients at this stage, even though efficacy evidence may be lacking. Device companies have little additional incentive to establish efficacy, a potentially expensive exercise and are more likely to target often limited resources at advertising. These aspects are in contrast to drug development where there is an inbuilt bias towards gaining phase 3 trial data because of mandatory regulatory requirements and often funding is available to facilitate this from the pharmaceutical industry.

To provide incentives for surgeons to evaluate these devices will require a change of emphasis from equipoise (i.e. both approaches equally effective) to uncertainty (i.e. don't know which is

best)[22] as well as rewarding such research. It will be important to understand the requirements that NICE and NHS Commissioners require for implementing innovation.

Knowledge gaps and recommendations

- To promote adoption of the IDEAL framework in the funding arrangements of technology trials.
- Develop a culture, and pathways, by which new technologies are introduced only once evidence has been established, and in doing so, incentivise research.

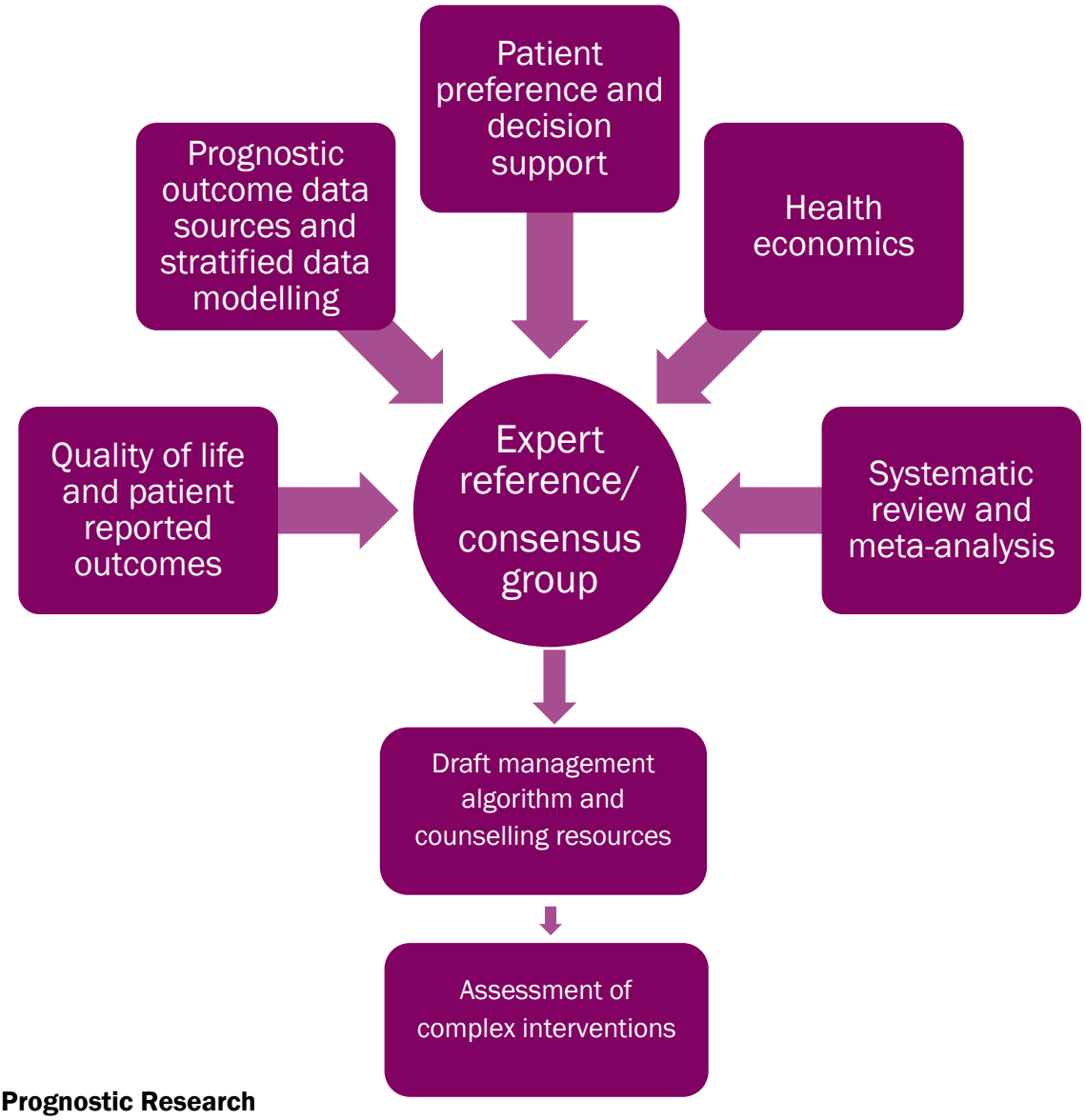
Selection of patients for surgery

Cancer treatment algorithms are increasingly complex and stratified by the stage and biology of the tumour as well as the physical fitness of the patient. Research which focuses on how to select the optimal treatment pathway for any given patient and disease profile is critically important in the field of surgery especially where surgical and non-surgical alternatives exist. An excellent example is breast cancer, where surgical options may include mastectomy, mastectomy and reconstruction (of varying types), breast conservation, oncoplastic conservation or, for the frailer older patient, primary endocrine therapy with avoidance of surgery altogether. The choice will be dictated by disease stage, patient and surgeon preference and disease biology. In some instances, all options will be potentially available. This workshop focused on research to facilitate optimal treatment selection.

This type of research encompasses a wide range of disciplines which are outlined below (and summarised in figure 2):

- **Prognostic and predictive outcome research** which may use data derived from a variety of sources, (observational data, RCTs, QoL research and health economics), analysed and validated using modelling methodology[23,24] to derive prognostic outcome models when multiple variables must be considered (stratified medicine).
- **The views and preferences of the patient** (and surgeon) using qualitative and mixed methods research, psycho-oncology techniques, decision science, patient-reported outcomes and quality of life research.
- **Data synthesis,** using a variety of methods**,** to construct complex management algorithms that are responsive to variations in disease stage, biology, patient fitness, preferences and outcomes (Figure 2).
- **Decision support tool development** to aid clinicians and/or patients. This may involve the development of online algorithms or patient counselling resources, which require rigorous development and validation.
- **Evaluation of complex interventions** to assess whether the stratified management algorithm or decision tool is effective in enhancing patient care and outcomes.

Figure 2. Schematic of processes involved in developing complex tools to select patients for surgery



Prognostic Research

Development of management algorithms requires detailed input and outcome data which may need to be derived from diverse sources including large observational datasets (which may be obtained from prospective or retrospective registry data or comprehensive cohort studies), often combined with more tightly focussed outcome data derived from randomised trials comparing specific sub-groups and interventions.

Data is usually analysed by developing a logistic regression model (using a range of statistical techniques) to determine the effect of a range of predictive and prognostic variables[23]. Modern techniques permit adjustment for missing data (very common in population registries) using techniques such as multiple imputation[25]. Observational data bias, such as selection bias, can also be adjusted for with techniques such as propensity score matching[26,27] to correct for baseline variable differences between treatment groups if non-randomised data has been used. In some cases, a specific management dichotomy may have randomised trial data to inform the effect size to be built into a model. The resulting model is then validated using a secondary dataset to ensure that the outcomes are appropriate for any given combination of variables[24].

Data from retrospective observational studies is valuable in the stratified medicine setting as it is often more reflective of 'real world' scenarios and reflects the complexity of disease and patient variables in contrast to RCT data which is highly selective. There are also huge numbers of potential patients in disease registries, with very long term follow up, which permits analysis of small sub-groups to permit a more stratified approach[28]. However, registry data access may be challenging to access due to regulatory issues such as data protection law and analysis may be complicated by or missing data in some fields or data that is not currently reliably collected by the NHS such as comorbidity and frailty data. There are ways to address these issues, such as multiple imputations and proxy measures.

Prospective observational studies have a much lower chance of bias and missing data but take much longer to conduct and are much more expensive to run, with direct follow up for many years and detailed baseline data.

Clinical Management Algorithm development

Having developed and validated a prognostic model, this may now be used as a component of a clinical management algorithm or other decision support tool. A variety of other data sources may be used to develop the pathway and generate an evidence summary. This should also include a systematic literature review and/or meta-analysis of published literature using published quality standards (PRISMA Standards[29]). The evidence summary and prognostic models are then reviewed by an expert reference group drawn from a spectrum of stakeholders including patient and public representatives.

Using such methods numerous prognostic and predictive models have been developed in surgery, many of which are regularly in clinical use (table 2).

Table 2: Predictive models used in surgery

PREDICT [30,31]	Online breast cancer prognostic and treatment benefit tool to help clinicians and patients make informed decisions about adjuvant chemotherapy and hormone therapy	Derived from cancer registry data on 5,694 women treated in East Anglia from 1999-2003.	Validated using a dataset of over 5000 breast cancer patients from the West Midlands Cancer Intelligence Unit and a large British Columbia dataset that had been previously used for a validation of Adjuvant! Online.
Adjuvant! Online [32,33]	Tool for assessing the 10 year risk of recurrence or death from breast cancer, when receiving specific adjuvant chemotherapy or hormone therapy.	The data derived from the large USA SEER database (Surveillance, Epidemiology and End Results Program).	Independently validated on patients from a large British Columbian registry.
P-POSSUM [34,35]	Tool for providing further information on risk in terms of morbidity and mortality of general surgical patients.	Prospective general surgery patients in the UK between August 1993 and November 1995.	This was then applied prospectively to the remaining 7500 patients arranged chronologically in five groups of 1500.
Alvarado [36,37]	A clinical scoring system used in the diagnosis of appendicitis.	Retrospective study of 305 patients hospitalized with possible acute appendicitis.	Several independent validation studies on small groups but with low predictive values

Rockall [38]	Identifies patients at risk of adverse outcome following acute upper gastrointestinal bleeding.	Based on prospective data collected as part of a national audit in four health regions in England	Validated using data collected during the second phase of a large national audit in 1994.

Patient Decision Support and Shared Decision Making

Another key area of selection of patients for surgery relates to understanding and supporting the preferences of the patient for any given treatment choice. Obviously a key component is to provide the patient with accurate, tailored outcome data on prognosis (derived from stratified prognostic models, as described above), risks of adverse events and quality of life[39]. To be valid, quality of life must be assessed using a specific tool developed to reflect the health impact of the treatment and disease under study of which there are a wide range[39].

These data may be used to develop decision support tools[40] that may have a clinician facing or patient facing output or both. Understanding the opinions, worries and preferences of patients is critical to the development of these tools and combinations of qualitative (usually interview based) and quantitative (bespoke or validated questionnaires) research methods may be required to explore these issues. Once a tool has been developed there are a number of research techniques and tools to validate it. These may include direct patient and clinician feedback, usage rates in trials or a real world setting (often as part of a formal process evaluation [41]) and a range of validated tools to assess patient knowledge, decision styles and decision regret and anxiety about the choice under study[42-45]. There is now an entire branch of medical research devoted to this and defined quality standards for the development and evaluation of decision tools (The International Patient Decision Aid Standards (IPDAS, 2012[46]).

Knowledge Gaps and Recommendations:

- Improved quality of registry data to include more detailed baseline data on comorbidity, frailty and other known risk factors to permit adequate case mix adjustment of outcomes.
- All surgical research should incorporate a qualitative patient element and quality of life analysis to ensure patient preferences and choices are adequately respected.
- Surgical trials should collect data on risk factors (age, frailty, comorbidity) in detail to permit stratified analysis of outcomes.

Window of Opportunity Studies

The ever-increasing numbers of novel anti-cancer agents being developed necessitates a clinical trial model to demonstrate clinical efficacy and utility in a timely, cost-effective manner. Window of opportunity (WoO) studies [47] provide such an opportunity, allowing the evaluation of the biological effects of new treatments, while simultaneously developing and validating appropriate biomarkers with clinical utility. A generic design highlighting the characteristics of WoO studies is shown in Figure 3.

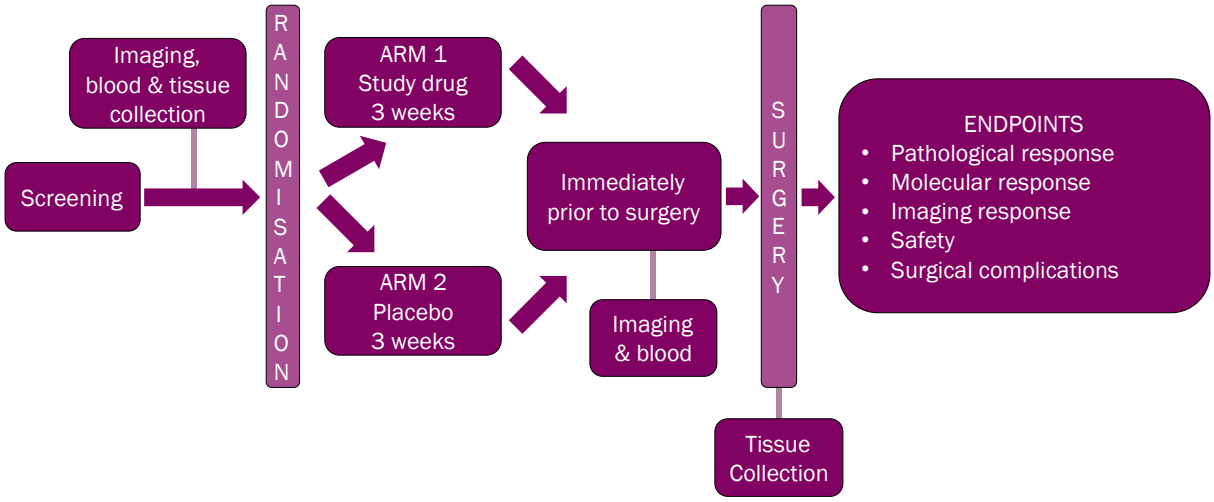


Figure 3: Typical WoO study design

Window of opportunity trials may greatly facilitate drug and biomarker development, improve our understanding of target effects. There are however possible safety and logistical implications with the potential of the window treatment introducing toxicities and/or a delay to surgery. The active input of surgeons is, however, vital to the success of WoO studies.

Issues key to successful study delivery of these WoO trials are:

- The identification of a clear biological hypothesis with clinical application which can be robustly tested within a WoO study.
- The involvement of surgeons in leading studies is crucial to successfully identifying and recruiting eligible patients, and within the tight timelines allowable such that the patient is receives definitive surgery in a timely manner.
- High quality serial biological samples are required in WoO studies, and the logistics of obtaining these necessitate good working relationships between surgeons and the research team.
- Toxicities in the peri-operative window need to be managed promptly, to minimise delays to surgery and surgical complications.
- Anticipate unexpected outcomes (e.g. pathological complete response), which may make the planned study primary endpoint difficult or even impossible to measure, and consider what alternative approaches may be required.

These issues are particularly pertinent in the context of immuno-oncology WoO studies, of which there are currently several in the portfolio (e.g. AMG319 in head and neck cancer). These types of study may create challenges in the management of unexpected immune toxicities, which will necessitate particularly close collaboration between the surgical and research teams. Furthermore, pre-analytical handling of biological specimens in such trials may need to be very specific; thus, it is important that the surgical teams are aware of the tissue requirements

associated with the study (e.g. the requirement for fresh tissue for flow cytometry) in order to ensure that the biomarkers under consideration can be accurately address. Robust biological endpoints reflective of meaningful clinical measures are required in immunotherapy WoO studies and many of these, such as changes in the composition of tumour immune infiltrates, require further validation.

Rather than a short course of treatment in a WoO study (to evaluate the biological effects of a novel treatment), some patients may receive a longer course of neoadjuvant therapy, with therapeutic intent, with the aim of inducing a complete response of their tumour to systemic therapy. Some patients however may have an incomplete response, and although these patients will proceed to resectional surgery, there is often a further window of opportunity between the completion of therapy and definitive surgery. This "post-neoadjuvant window" has the potential for developing a clinical trial platform using biopsies of residual disease after neoadjuvant treatment to evaluate the biological efficacy of novel agents in a targeted setting prior to definitive surgery.

Knowledge gaps and recommendations:

- To promote window of opportunity studies within surgical oncology, but recognise their resource-intensive design and need for adequate resource.
- To reinforce links between surgery, molecular biology, molecular pathology, pharma and medical oncology in order to facilitate trial design and delivery in the window of opportunity.

Surgery for Metastatic Disease

Surgery for metastatic cancers needs to consider three fundamental issues: (1) the control of the primary tumour, (2) imaging of metastatic burden, and (3) treatment of the metastatic sites. Advances in systemic drug therapy has resulted in many more patients who have stable metastatic disease, where surgery is now considered, however the overall benefit of such surgery is as yet not clear.

The role of surgical removal of the primary lesion in solid malignancies has been demonstrated previously, with benefits already rationalized in renal and ovarian cancers via level 1 evidence from EORTC and SWOG trials and a Cochrane review, respectively[48-50]. With the advent of minimally invasive surgery, and especially robotic technology, the morbidity of major cancer surgery is decreased, and nowhere has the switch from open to robotic surgery been more pronounced than in radical prostatectomy[51]. This has led to recent observational series demonstrating the safety and technical feasibility of robotic prostatectomy in metastatic disease[52], and recent epidemiological data support its investigation in patients with a limited metastatic (oligo-metastatic) load[53,54]. A randomized controlled feasibility study in men with oligo-metastatic prostate cancer has now opened in the UK using an embedded qualitative recruitment investigation to optimize randomization (TRoMbone; ISRCTN15704862).

Imaging the metastatic burden is crucial to determine which patients might most benefit from treatment of the primary lesion, and to allow targeting of metastatic sites for therapy. Conventional imaging modalities like CT and bone scintigraphy are being challenged by novel PET tracers and whole-body MRI. Future randomized trials need to incorporate imaging sub-studies to assess comparative effectiveness of diagnostic imaging tools and accurately define disease burden and site.

Metastasis-directed therapy (MDT) can be performed by surgical or radiation-based delivery. Stereotactic body radiotherapy (SBRT) is expanding in the NHS by Commissioning Through Evaluation and randomized trials are currently accruing in the metachronous oligo-metastatic setting in which a disease-free interval between primary therapy and recurrence has occurred. In the second half of the workshop we explored surgery as MDT for liver and non-liver (focusing on lung, bone, and brain) metastases. Cognisant of the recent closure of the PulMiCC trial for lack of recruitment, a number of potential themes for trials in this setting were highlighted, addressing areas of unmet clinical need.

Knowledge gaps and recommendations:

- Meta-analysis of resection for non-colorectal liver metastases.
- Support for clinical trials exploring the impact of loco-regional treatment in the setting of liver metastases.
- A national registry on surgery for bone metastases, as these cases are not discussed in a defined MDT and generally escape systematic analysis.
- Brain metastases should not be excluded by future studies in the metastatic setting.
- Future trials should incorporate sub-studies of novel imaging to refine the diagnosis of metastatic burden.

Conclusions

The Future of Surgery initiative led by the NCRI has concluded, identifying important gaps in clinical knowledge and giving direction to themes for further clinical trials. Additionally, some recommendations have been made that are common to many surgical disciplines in trials methodology, highlighting the complex and challenging nature of surgical research.

Some gaps in clinical evidence cannot be adequately addressed using randomised trials, and there is a need to consider alternative methodologies such as cohorts and registries to collect important data in rare diseases, emergency presentations, frail or elderly patients and such previously un-researched but important areas of oncology where surgeons contribute.

By working closely with the surgical research community trial funding bodies can support and nurture surgical research in the UK in the context of surgery being a complex intervention with differences in phases of researching new operations and devices.

Similarly, multidisciplinary research can place great demands on the clinical research team, emphasising the resource-intensive nature of surgical trials, for example, window of opportunity studies.

Lastly, new opportunities for effective cancer surgery have arisen from the promising outcome of effective systemic therapies and minimally invasive surgery, all requiring novel approaches to generating reliable evidence, some of which may span several tumour types and anatomical sites.

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Appendix one - authorship

Seema Alexander	NCRI
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Sue Ward	University of Sheffield
Lynda Wyld	University of Sheffield

Appendix two – "Trials are only as credible as their endpoints" agenda

4 May 2016

10.00	Registration and tea & coffee	
10.30	**Welcome address**	Angus McNair
10.35	**A surgical trial is only as credible as its endpoints**	Kristian Brock
11.00	**The PATHOS trial**	Terry Jones
11.15	**Discussion** • *What are the key challenges in selecting and measuring outcomes in surgical trials?*	
12.00	Lunch	
12.45	**The role of feasibility studies in surgery** **Part 1: The LORIS trial**	Adele Francis
13.10	**Part 2: Using feasibility study outcomes to inform the main trial**	Jane Blazeby
13.35	**Discussion** • *What outcomes are important in feasibility studies to inform the design and delivery of the main trial?*	
14.30	Tea & coffee	
14.45	**Outcomes in early phase studies of novel surgeries**	Simon Bach
15.00	**Discussion** • *What outcomes are important to assess in early phase surgical studies?*	
15.30	**Actions, next steps and summary**	Angus McNair
16.00	Close	

Appendix three – "Technology trials in surgical oncology" agenda

20 September 2016

10.00	Registration and tea & coffee	
10.30	**Welcome address**	Stephen Price
10.35	**IDEAL recommendations for surgical trials**	Peter McCulloch
11.00	**First in man studies – High-intensity focused ultrasound (HIFU)**	Hashim Ahmed
11.15	**Non-randomised designs & the learning curve in technology trials**	Jonathan Cook
11.45	**Assessment: RCT in surgery – The ORANGE II Trial**	John Primrose
12.00	**iKnife: Developing a new surgical tool**	Zoltan Takats
12.15	**iKnife: Determining tumour margins in gliomas**	Babar Vaqas
12.30	Lunch	
13.15	**Regulation of medical devices and technologies**	Peter Jarritt
13.30	**Working with Industry – Surgical Technology Evaluation Portal (STEP)**	Ravi Chana
13.45	**Parallel Sessions: Roadmapping**	
	Early Phase Surgical Trials	Stephen Price
	Robotics in Surgical Oncology	David Jayne
15.00	Coffee	
15.15	**Panel Discussion: How Can We Incentivise Surgeons to Evaluate New Technology?**	
15.45	**Summary and next steps**	Stephen Price
16.15	Close	

Appendix four – "Selection of patients for surgery" agenda

23 November 2016

9.30	Registration and tea & coffee	
10.00	Welcome address	Riccardo Audisio and Lynda Wyld
10.05	Overview of the issue and plan for the day	Lynda Wyld
10.30 - 12.30	**Patient selection for Surgery: Data sources and algorithm design**	
10.30	Complex risk stratification: use of modelling.	Sue Ward
10.55	Cohort and registry study methods: correcting and stratifying for patient and disease variables	Rebecca Birch
11.20	Cohort data collection: role of the trainees collaborative	Matt Lee
11.45	Design of management algorithms and on line tools	Jenna Morgan
12.10	Discussion	
12.30	Lunch	
13.00 – 14.30	**Assessment of fitness and frailty and the role of pre- and re-habilitation**	
13.00	Aging, geriatric syndromes, frailty and treatment tolerance	Margot Gosney
13.20	Research in practice: the PACE and PreOp studies, and beyond…	Riccardo Audisio
13.40	Risk scoring in hepatobiliary surgery	Declan Dunne
14.00	Prehabilitation in colorectal cancer surgery	Jon Lund
14.20	Discussion	
14.30	Coffee	
14.45 – 16.15	**A Patient decision making: supporting informed choice**	
14.45	Quality versus quantity of life in decision making: Trade-offs, quality versus quantity and drivers of choice.	Zoe Ellen Winters
15.10	Development and use of decision support tools	Adrian Edwards
15.35	Qualitative and mixed methods research and how to apply them in surgery	Georgina Jones
16.00	Overview of the day	Faculty and chairs
16.30	Close	

Appendix five – "Window of Opportunity Studies" agenda

17 January 2017

9.30	Registration and tea & coffee	
10.00	Welcome address	Stuart McIntosh
Pre-surgical trials		
10.10	Pre-operative and window studies: challenges and opportunities	Christian Ottensmeier
10.30	Window studies from the surgeon's perspective:	
	• EPHOS-B	Nigel Bundred
	• AMG319	Emma King
11.00	Discussion	
11.30	Coffee	
Surgical trials – how to evaluate the extent of surgery in clinical trials		
11.50	Clinical trial design for evaluating extent of surgery	Mike Clarke
12.10	Lessons from trials evaluating the extent of surgery	
	• POSNOC & ATNEC	Amit Goyal
12.30	A.I and surgical decision making: de-escalating surgery in ovarian cancer	Richard Edmondson
12.45	Discussion	
13.15	Lunch	
14.00 – 16.30 Monitoring of response to treatment and surgical planning in pre-surgical trials		
14.00	Monitoring treatment response and surgical planning in upper GI cancer	Tim Underwood
14.20	STAR-TREC trial	Simon Bach
14.40	The "post-neoadjuvant window of opportunity"	Sheeba Irshad
15.00	Discussion	
16.00	Actions and Summary	
16.30	Close	

Appendix six – "Surgery for Metastatic Disease" agenda

21 March 2017

9.30	Registration and tea & coffee	
10.00	Welcome address	Hasan Malik, Prasanna Sooriakumaran
Session 1: Surgery to the primary		
10.05	Introduction	Prasanna Sooriakumaran
10.10	Kidney	Ravi Barod
11.25	Prostate	Prasanna Sooriakumaran
11.40	Ovarian	Pubudu Pathiraja
Session 2: Imaging of metastatic burden		
10.55	Stereotactic body radiotherapy (SBRT) as metastasis-directed therapy	Maria Hawkins
11.10	Imaging of metastatic buden	Nina Tunariu
11.25	Coffee	
Session 3: State of the art, update on current trials and potential gaps in current practice		
11.45	Introduction	Hassan Malik
11.50	Non-colorectal non-neuroendocrine liver metastasis	Zaed Hamady
12.05	Pulmonary mestastases	Michael Shackcloth
12.20	Brain metastases	Michael Jenkinson
12.35	Proximal femoral metastases	Robert Ashford
12.50	Lunch	
13.35	Introduction to breakouts	Prasanna Sooriakumaran
13.40	Breakout sessions	
14.50	Coffee	
15.10	Feedback from breakout sessions	
16.50	Conclusions and next steps	Hasan Malik, Prasanna Sooriakumaran
16.30	Close	

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