Platform Trials for Anaesthesia and Perioperative Medicine

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Summary

Large randomised trials provide the most reliable evidence of effectiveness of new treatments in clinical practice. But the time and resources required to complete such trials can be daunting. An over-arching clinical trial platform focussed on a single condition or type of surgery, aiming to compare several treatments, with an option to stop any or add in new treatment options, can provide greater efficiency. This has the potential to accelerate knowledge and identify effective, ineffective, or harmful treatments faster. The master protocol of the platform defines the study population(s) and standardised procedures. Ineffective or harmful treatments can be discarded or study drug dose modified during the lifecycle of the trial. Other adaptive elements that can be modified include eligibility criteria, required sample size for any comparison(s), randomisation assignment ratio, and the addition of other promising treatment options. There are excellent opportunities for anaesthetists to establish platform trials in perioperative medicine. Platform trials are highly efficient, with the potential to provide quicker answers to important clinical questions that lead to improved patient care.

Large randomised trials are widely recognised as providing the most reliable evidence of effectiveness of new treatments in clinical practice.[1, 2] But the effort, resources, and time required to design the trial and gain funding, establish infrastructure and a network of sites, complete governance requirements, and then conduct the trial, analyse and publish the results, can take many years and is often too overwhelming. Adoption into clinical practice takes longer still.[3] Given there are many clinical questions that need to be answered and too few opportunities for large-scale clinical trials,[4, 5] innovative trial designs offer solutions.[6, 7]

Anaesthesia-perioperative clinical trial networks greatly facilitate the conduct and efficient completion of large clinical trials.[8, 9] With experienced triallists overseeing the design and conduct of the trial(s), and centralised governance oversight and infrastructure (database build, web-based randomisation, data management, statisticians), such trials can be more easily established and completed. These features can reduce research waste.[9, 10]

But the efforts needed to successfully complete any single trial should not end at publication – the acquired knowledge, infrastructure and trial network, and momentum, should be harnessed to address new clinical questions *as soon as practicable*. The lead-time required to establish the next conventional clinical trial is a costly hindrance to the ongoing discovery of new knowledge in our specialty.

Platform trials

An over-arching clinical trial platform focussed on a single condition or type of surgery, aiming to compare several treatments, with an option to stop any or add in new treatment options,

can provide greater efficiency (Fig. 1).[11, 12] This has the potential to accelerate knowledge and identify effective, ineffective, or harmful treatments faster.

The master protocol of the platform defines the study population(s) and has standardised trial procedures and data collection, with a (sometimes complex) statistical analysis plan.[11-13] Eligible participants are simultaneously randomly assigned to one or more experimental treatments or to a common comparator groups. The standardised trial procedures are designed to allow robust comparisons of several treatment options within the overarching platform. The sharing of a single control group decreases the overall required sample size compared with a series of conventional trials, reducing time to completion and saving on costs. Ineffective or harmful treatments can be discarded or study drug dose modified during the lifecycle of the trial. Other adaptive elements that can be modified include eligibility criteria, required sample size for any comparison(s), randomisation assignment ratio, and the addition of other promising treatment options.[12, 14]

Design features of platform trials include: (i) domains – typically a drug or treatment class, (ii) strata – defined by baseline characteristics that may have different treatment effects across each, (iii) states – describing the patient's condition which may change over time, sometimes used as a component of domain eligibility.

Readers should note that in platform trials with staggered entry and exit of experimental treatments and an ongoing control arm, comparisons may be confounded by changes over time in the control group. However, incorporating all randomised control subjects with statistical adjustment for temporal drift can provide superior estimations of treatment effects

and favourable testing properties (unbiased estimates with high precision, low type I error and high power) compared to analyses either limited to concurrent controls or using pooled controls.[15] This, however, would depend on the nature of the time trends. Comparisons of two or more active interventions may require more complex considerations during analysis. There is currently much debate and ongoing research regarding this issue.[16]

Examples of platform trials in clinical medicine include the ongoing systemic therapy for advancing or metastatic prostate cancer (STAMPEDE) trial,[17] the randomised evaluation of COVID-19 therapy (RECOVERY) trial,[18] and reduction of surgical site infection using several novel interventions (ROSSINI 2) (ref: https://clinicaltrials.gov/ct2/show/NCT03838575).

and the randomised embedded multifactorial adaptive platform for community-acquired pneumonia (REMAP-CAP) trial.[19]

Monitoring and interim analysis

Large clinical trials commonly utilise interim analyses to check for larger-than-expected treatment effects, unexpected harm, or futility.[20] Platform trials build on this concept by prespecifying thresholds for platform conclusions and adaptations to be evaluated at regular intervals, which can potentially allow results to be declared when statistical thresholds are met, rather than once a fixed sample size has been achieved and followed up. If one or more treatment groups have a more favourable estimate of treatment effect at an interim (adaptive) analysis, then a modification to the random assignment proportions favouring this group can be implemented. This feature, known as *response-adaptive randomisation* (RAR), provides a participation benefit, and protects clinical equipoise for both participants and

clinicians, and generally may make a trial more efficient.[21] RAR shows most benefit when more than 2 arms (per domain) are considered. However, evolving trends in treatment effect of open-label interventions may be exposed resulting in potential bias to the treatment effect estimates. RAR must be implemented with care because statistical power can be reduced if randomisation proportions are allowed to diverge excessively.

Statistical considerations for platform trials

Analytic techniques may use conventional frequentist statistics,[17, 18] or Bayesian methods[19] where updated posterior probabilities may trigger an adaptive step.[22] Simulations to assess the impact of adaptations are commonly used at the design stage, and transparency in these processes is encouraged.[23, 24]

Frequentist approaches typically involve null hypothesis testing, as well as calculated P values and confidence intervals for inference. Bayesian methods incorporate existing information or beliefs about the unknown parameters of interest (e.g. treatment effect) and uncertainty around these estimates into the analysis by specifying initial probability distributions before collecting data (called “priors”). Then, as new data are observed, the probability distributions of the model parameters are updated, producing “posterior distributions”. Conclusions from the data are then drawn using the posterior distributions. The Bayesian approach provides a principled framework for performing interim analyses in a clinical trial as information accumulates. For a more detailed description of frequentist and Bayesian approaches we refer the reader to Ryan and colleagues[25] and references therein.

The frequentist approaches to platform trials typically focus on strict control of type I error (either pairwise or familywise/overall) or false discovery rates, and are often extensions of the "multi-arm multi-stage",[26] or the group sequential,[27, 28] approach. These designs have generally used equal randomisation allocation ratios amongst experimental arms (sometimes with a higher allocation to the control arm to maintain power). Examples of platform trials that have been conducted in the frequentist framework include STAMPEDE,[17] SOLIDARITY,[29] and RECOVERY.[18]

Many platform trials prefer to use Bayesian statistical methods[30] as they are naturally suited to performing repeated analyses and adaptations, and allow for incorporation of prior information and information borrowing (e.g., across patient subgroups, use of non-concurrent controls). Due to their flexibility and incorporation of complex features, the operating characteristics of Bayesian designs are determined by simulations. Some examples of Bayesian platform trials include REMAP-CAP,[19] GBM-AGILE,[31] and TOGETHER.[32]

There are several different frameworks for conducting platform trials, even within each of the Bayesian and frequentist paradigms. Some platform trial designs study multiple arms in a single domain, and may add or remove treatments over time (e.g. ROSSINI 2,ref STAMPEDE,[17] TOGETHER[32]). Other designs allow patients to be randomly assigned to treatments across multiple domains (with additional domains potentially being added over time), using partial factorial designs, so that different regimens/combinations of treatments can be compared (e.g. RECOVERY, [18] REMAP-CAP[19]). Some platform trial designs may also include different patient populations, which may (or may not) have differing treatment options available.

Sample size and power

Unlike traditional clinical trials, adaptive platform trials often do not have a fixed sample size that determines when the study will end. It may be difficult to prespecify a sample size for a platform trial since not all of the study interventions that are to be included in the platform will be known at the start of the trial. Platform trials usually do not fix the total number of experimental arms that are to be used for the duration of platform, although the number of arms at a given time point or within a domain may be fixed. Instead, they can allow new candidate treatments to enter the trial as they become available and may also permit removal of trial arms (Fig. 1). Adaptive platform trials are often "perpetual" in that they have no fixed ending, and may continue to add domains and/or interventions, subject to availability and funding. One of the features of a perpetual platform trial may also offer is the updating of a control arm once an efficacious arm has been identified (e.g., STAMPEDE[17]), subject to practicalities and ethics. It is also possible to remove the control arm of a specific domain of a platform (e.g. REMAP-CAP COVID-19 immune modulation domain[33]).

Sample size or power calculations may be performed to provide an initial guide to the maximum number of participants that are required to answer a particular question - for instance, a particular treatment comparison within a domain or substudy - and individual domains or treatment comparisons may have a fixed or maximum sample size prespecified (e.g., ROSSINI 2,ref TOGETHER,[32] I-SPY 2[34]). Extensive computer simulations are usually required to study the trial design's operating characteristics, including demonstration of the control of type I error; this however is challenging and there is no consensus on how this is best done. Additional simulation work is likely to be required once the trial is in progress as more information becomes known about the recruitment rates, potential new treatments,

and other trial assumptions. Alternatively, some platforms (mostly for COVID-19 treatments) have begun without a prespecified sample size and continue to recruit to a treatment arm or domain until a predefined statistical trigger has been met, or if external evidence or safety concerns trigger arm closures (e.g., RECOVERY, [18] REMAP-CAP, [19] SOLIDARITY[29]).

Statistical trigger

Adaptive platform trials perform prespecified repeated analyses (adaptive analyses) using the current data to update the statistical model parameter or test statistic estimates. A statistical trigger typically takes the form of a cut off on a quantity of interest on which a decision is made.

Platform trials conducted using the frequentist approach might define the statistical trigger in terms of test statistics and P values akin to boundary crossing in group sequential designs. Alternatively, they may require experimental treatments to pass a series of hurdles based on particular effect sizes at the interim analyses (e.g. STAMPEDE[17]) as proof of efficacy. Failing this, the experimental arms are stopped. Bayesian platform trials may define statistical triggers in terms of posterior probabilities, such as the posterior probability that the relative risk is less than 1, and if this probability exceeds a prespecified threshold then the trigger is met. Simulations are used to determine suitable thresholds for these statistical triggers, and appropriate timing of the adaptive analyses.

The consequences of a statistical trigger being met may include: discontinuing an arm for efficacy (“graduating”) or futility, two treatments being declared equivalent, an intervention being declared non-inferior, an intervention being declared superior to control, or a

treatment being declared the “best” out of all the treatments studied in a domain. Statistical triggers may also result in the closure of a domain, the transition from one study phase to the next, or ceasing certain treatments to be available to particular patient subgroups. External evidence may also trigger decisions, such as stopping treatment arms for safety or overwhelming efficacy (e.g. REMAP-CAP antiviral and corticosteroid domains[35, 36]).

The REMAP-CAP trial

One of us (CM) is a member of the steering group of REMAP-CAP. REMAP-CAP was established by an international group of intensive care clinical triallists following the 2009-10 H1N1 influenza pandemic during which no substantive therapeutic trials were conducted. Establishing a platform trial with regular adaptive analyses in a Bayesian framework[37] which could adapt quickly in the event of a pandemic was considered the best design to address this deficiency. Severe community-acquired pneumonia was chosen as the study condition being both an important inter-pandemic illness with unresolved treatment questions and the likely clinical syndrome of a future pandemic.

The platform was first funded in the EU (including the UK) and then sequentially in Australia, New Zealand, and Canada, and is led by an inclusive International Trial Steering Committee with regional coordinating centres in Utrecht, Melbourne and Toronto. Recruitment commenced in 2016 and included domains evaluating empiric antibiotics, extended macrolide treatment as an anti-inflammatory therapy, corticosteroids, and oseltamivir. The flexible design and analytical plan allows sites to choose the domains and interventions in which they participated (based on local equipoise and intervention availability) and the eligibility and electronic case report form systems present parsimonious questions

appropriate to regional ethical approval and site choices. Domain participation requires the selection of at least 2 interventions for randomisation. Statistical thresholds for superiority, efficacy, equivalence, futility and inferiority were set prospectively.

In February 2020, the planned adaptation for a pandemic was implemented with a separate pandemic stratum and statistical model using a composite ordinal scale primary outcome of hospital mortality and ICU organ support-free days to day 21. COVID-19 treatment domains were developed with recruitment commencing in March and the number of participating sites rapidly expanded to over 300 intensive care units in more than 15 countries. The combination of a relatively homogeneous disease, a sensitive primary outcome, and high patient numbers over the first year of the pandemic enabled posterior probability thresholds to be quickly reached in several COVID-19 domains.

External evidence of benefit in June 2020 led to the discontinuation of steroid assignments in the pandemic stratum prior to reaching a statistical trigger with analysis confirming a 93% probability of superiority of fixed-dose hydrocortisone and identifying a steroid class effect.[35] In the immune modulation domain, tocilizumab triggered for superiority in November 2020 and another interleukin-6 receptor antagonist, sarilumab, in January 2021.[33] In a prospective multi-platform design with 2 other trials, prophylactic therapeutic-dose anticoagulation in the critically ill reached futility in December 2020 with a strong signal for harm,[38] but recruitment seamlessly continued in the non-critically ill for another month until reaching superiority.[39]

In the COVID-19 antiviral domain, hydroxychloroquine and lopinavir/ritonavir were both found to be harmful in the critically ill,[36] while convalescent plasma[40] and antiplatelet

therapy[41] reached futility triggers in January and June 2021 respectively. A strong signal for possible benefit of convalescent plasma in the immunosuppressed has led to the domain being re-opened for this subgroup. Other domains (e.g. lower dose anticoagulation, angiotensin converting enzyme/renin-angiotensin system inhibitors, vitamin C and simvastatin) are continuing to recruit or are currently being analysed after reaching statistical triggers. In response to COVID-19, REMAP-CAP has demonstrated the efficiency and power of an adaptive platform in a global collaboration but its operational and analytic complexity is significant.

Challenges and potential disadvantages

Platform trials will need substantial set up and maintenance costs, but there are likely cost-efficiencies once established. Very few national medical research funding agencies have systems in place to fund an ongoing platform trial, although we anticipate that this will change in the near future. Research governance processes must consider the ongoing changes to study treatments and their implications for patient consent and adverse event reporting. Patients may be eligible for some treatment arms but not others, or participating sites may decide to not participate in some treatment arm options – this can be managed but could be confusing for study site clinicians and do add complexity to data management and analysis. The inclusion of new treatment arms with and an ongoing control arm introduces potential bias and confounding because of changes in the disease of interest or in practice. How to best deal with this continues to be debated in the biostatistical and clinical trials literature.[16] These biases could distort RAR. The relative benefits of conventional frequentist or Bayesian methods are also debated, and it is likely that either approach may be preferable for specific conditions.[25] The design, sample size and other operating characteristics should be

underpinned by extensive computer simulations, and further simulations are likely to be required as more information becomes known though the trial.

Opportunities for anaesthesia and perioperative medicine

Some adaptive trials are now being conducted in perioperative medicine,[42-44] and mainly focussed on simple adaptions. Platform trials have not yet been implemented but their potential is immense. There are many areas of perioperative practice that would be well-suited to platform trials (Table 1). Note that adaptive designs need a relatively short time to observe a primary outcome, adding to their potential value in perioperative medicine. We present below two potential examples of such trials.

A potential platform trial for postoperative delirium

Delirium is a common neuropsychiatric syndrome defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as disturbance of attention, awareness and cognition which develops over a short period of time, which represents a change from baseline and tends to fluctuate over the course of the day.[45] Postoperative delirium (POD) delays mobilisation and discharge, and increases the need for social input. POD is also associated with higher mortality, poorer long-term functional outcomes, institutionalisation, anxiety and depression.[46-51] There is also emerging evidence that suggests that POD and other perioperative neurocognitive disorders can persist in some patients whose risk of dementia and cognitive dysfunction is also increased.[52, 53] The negative sequelae of POD is recognised, clinical care has so far failed to universally adopt an evidence based approach in both its prevention and management.

Systematic reviews have highlighted promising interventions that could be tested (Fig. 2).[54, 55] Potential pharmacological interventions include the use of intraoperative electroencephalogram monitoring,[56] depth of anaesthesia-guided anaesthesia,[57] total intravenous anaesthesia,[58, 59] steroids[60] and dexmedetomidine.[61] Non-pharmacological interventions include cognitive prehabilitation,[62] and patient and family education.[63] Multiple interventions can be tested simultaneously in patients according to their stratified risk.

Whilst our understanding of POD syndrome continues to develop, the complex aetiology of delirium as a syndrome becomes ever apparent. Direct brain insults such as hypoxia, hypotension, medications and metabolic derangement can provoke delirium in the perioperative setting, which is often worsened by acute stress response brought on by sepsis, inflammation and surgery.[54, 64] It is perhaps unsurprising that clinical trials which focused on single interventions applied to whole patient group have so far been unable to provide a panacea to delirium. Two recent large randomised controlled trials that compared the impact of general versus regional anaesthesia in patients with hip fractures failed to demonstrate significant difference in incidence of POD.[65, 66] In comparison, complex, multi-component interventions targeting specific risk factors were able to reduce incidence of delirium in medical inpatients and patients following elective and hip fracture surgery.[67-69] It is therefore not unreasonable to hypothesise that 'one size does not fit all', and a more targeted approach is required to identify those who may be at risk of developing POD and what specific targeted intervention would be effective.

A platform trial design can allow evaluation of multiple interventions to prevent and manage delirium to be tested simultaneously in a cohesive and systematic manner.[55] There are key

study design considerations. Firstly, a potential platform trial for POD must include patients who are at risk of developing the condition, and those with pre-existing cognitive dysfunction or dementia who arguably are most vulnerable should not be excluded. Risk stratification should include frailty, sarcopaenia, and preoperative cognitive screening.[56, 70] The role of preoperative screening using inflammatory biomarkers remains unclear and cannot be recommended.[71] Such a trial could have separate strata for patients that do in fact develop POD that then become eligible for other domains/treatments.

A potential platform trial for surgical site infection

Surgical site infections (SSIs) are a major and frequent postoperative complication.[72] SSIs have been shown to increase hospital stay, healthcare costs, and patient disability.[73, 74] The World Health Organization (WHO),[75] US Centers for Disease Control and Prevention (CDC),[76] UK National Institute for Health and Care Excellence (NICE),[77] and the Surgical Care Improvement Project (SCIP),[78] are but a few of the many organisations to issue evidenced-based recommendations designed specifically to reduce the frequency of SSIs (Table 2). Indeed, the adoption of these bundled processes of care have been shown to reduce the incidence of SSIs.[79] The major problem with these recommendations is that they are not easily and/or uniformly employed across the surgical spectrum.[80] One possible reason for hesitancy may be that the strength of evidence is generally low, and often the recommendations from one group conflicts with another. Despite the long history of these recommendations, recent clinical trials show that the incidence of SSIs remains unacceptably high.[81, 82]

There are a number of SSI recommendations that relate specifically to anaesthesia and perioperative medicine (Table 2). Most are “conditional” and so require further study, or are

otherwise derived from small trials. There is an urgent need to improve our understanding of effectiveness of these interventions. The most recent WHO global guidelines for the prevention of SSI address the following domains:[75]

1. Immunosuppressive medications

   The WHO meta-analysis includes 8 studies,[75] but these studies pertained only to patients with rheumatoid arthritis and only evaluated methotrexate and TNF inhibitors. Overall, the included studies covered a limited number of events and the results had very wide confidence intervals (CIs). There were no randomised trials including patients receiving long-term steroid therapy. However, several retrospective analyses of National Surgical Quality Improvement Program (NSQIP) data show increased SSIs in these patients.[83] It is unclear how an effective mode of discontinuing long-term steroids would work, or even if it is practical. Furthermore, any such intervention would run the risk of exacerbating the underlying disease being treated with steroids. Short-term use does not increase surgical site infections.[81] In addition, there are limited data to guide perioperative management of patients being treated with the newer biologics like monoclonal antibodies.[84, 85]

2. Antibiotic prophylaxis (timing)

   Overall, 13 observational studies comparing different timing intervals for surgical antibiotic prophylaxis with an SSI outcome have been identified and collated meta-analytically.[75] There are no randomised trials addressing this topic. The body of retrieved evidence focused on adult patients; no study was available in the paediatric population. Overall, antibiotic prophylaxis given after incision compared to before

incision doubled the odds of SSI. Administration more than 120 min prior to incision resulted in a 5-fold increase in the odds of SSI. The WHO recommendation is based on very low-quality of evidence. The analysis shows that administration within 30 minutes prior to incision had neither benefit or harm related to the reduction of the SSI rate when compared to administration within 60 to 30 min prior to incision. This WHO meta-analysis excluded a retrospective analysis in over 28,000 patients by Koch and colleagues,[86] which found the lowest prevalence for infection when antibiotic prophylaxis was administered 15 minutes before incision; the risk increased to 2.2% when antibiotic prophylaxis was administration more than 45 minutes before incision and to 2.8% at 60 min before incision. Importantly, the timing recommendation varies (60 or 120 min) in different guideline documents.

3. Intensive glucose control

   A meta-analysis of 15 studies found that blood glucose target levels of less than 150 mg/dl (8.3 mmol/l), using an intensive protocol in the perioperative period, reduced SSI.[87] The intensive protocol found an inherent risk of hypoglycaemic events but without a significant increase in serious adverse events. The risk of bias in the included studies was serious, as many variables were scored as unclear or even high. No study had SSI or wound infection as the primary outcome. In addition to being low quality these studies lack generalisability as all studies were conducted primarily in cardiac or major abdominal surgery and all patients were admitted to an ICU postoperatively.

4. Goal-directed fluid therapy

Evidence assessed by the WHO included 3 types of studies: (i) goal directed fluid therapy (GDFT), (ii) liberal vs. restrictive fluids, and (iii) hypotension avoidance studies. Overall, a low quality of evidence from randomised trials shows that intraoperative GDFT has a significant benefit in reducing the SSI rate compared to standard fluid management.[75] The systematic review found that an algorithm to dictate fluid administration (GDFT) reduced SSI rates compared to standard management. Five studies comparing restrictive fluid management vs. *standard fluid management* showing no difference in the risk of SSI. The quality of evidence for these two comparisons was low due to risk of bias. The definitions of restrictive fluid therapy and the algorithms of GDFT are heterogeneous. The above analysis does not include the results of the high-quality RELIEF trial which found that a liberal fluid strategy (11 ml/kg/hr) reduced SSI when compared to a restrictive strategy (6.5 ml/kg/hr).[88] Finally, some studies found that avoiding hypotension reduced postoperative infection.[89] The results of the soon to be completed OPTIMISE ll trial, where cardiac output is supported with the use of inotropic agents, is expected to further inform this knowledge base.[90]

5. Normothermia

The 2 included studies reported independently that systemic body warming has significant benefit compared to no warming in reducing SSI following surgery.[75] Both studies had a relatively small sample size and populations undergoing only clean or clean-contaminated surgical procedures. Furthermore, the analysis does not include the recently published PROTECT trial where, in 5000 patients there was no difference in SSI rates between the warm patients (36^{o}) and cooler patients (34.5^{o}).[90] When this

trial is included meta-analytically the effect of a temperature >36^{o} is negligible (OR 0.98, 95% CI 0.83-1.25). Interestingly, in the PROTECT trial there was no advantage for blood transfusion, myocardial injury, or death.

6. Perioperative oxygenation (fraction of inspired oxygen 80%)

   This remains a contentious issue.[91-93] An updated (2019) meta-analysis of 17 studies in almost 8000 patients was conducted for the WHO.[94] Overall, no evidence for a reduction of SSI after the use of high oxygen fraction was found. In a subgroup of 6000 patients with tracheal intubation, a reduction in the incidence of SSI was seen (OR 0.80, 95% CI 0.64-0.99). This WHO recommendation is supported by the strongest evidence base.

~~*Factors associated with postoperative infection not addressed in guidelines:*~~

~~7. Anaesthesia provider/workspace hygiene~~

~~The WHO recommendations on hand hygiene do not specifically target anaesthesia providers. There is however a substantial body of evidence highlighting the role of anaesthesia providers in perioperative infection transmission.[95] The inability to maintain a clean workspace occurring during induction and emergence has been shown to contaminate the anaesthesia provider's hands and it must be acknowledged that anaesthetists have a poor record when it comes to regular and timely hand hygiene (i.e. before *and after* aseptic interventions).[96] Barriers to effective hygiene include lack of access to hand sanitisers, and education. Another potential infection control consideration could be an evaluation of the value of surgical masks.[97]~~

~~8. Regional anaesthesia~~

~~The use of neuraxial anaesthesia, compared to general anaesthesia, has been associated with a significant reduction in incidence of postoperative SSIs.[98, 99] In contrast however, the recently published REGAIN trial did not find lower infection rates in patients receiving spinal anaesthesia.[100]~~

SSI remains a major perioperative issue, but there are important knowledge gaps and many guideline recommendations for numerous interventions based on weak evidence. This is an ideal situation for a multinational platform trial in which several clinical trial networks can work off the same master protocol and share resources. Such a platform could initially have three embedded domains for evaluation: (i) an anaesthesia-practice hygiene intervention, (ii) a pragmatic comparison of when to administer (and when to continue) antibiotic prophylaxis, (iii) a comparison to ensure maintenance of organ perfusion, via some form of fluid therapy regimen. Domain adaptions could include patients with diabetes to evaluate intensive perioperative blood glucose, and immunosuppressive therapy used for disease states such as chronic pulmonary disease, inflammatory bowel disease, arthritis, graft vs. host disease, or haematological cancers. Future interventions could include regional anaesthesia, blood transfusion, and immune modulators.

Finally, any in-depth analysis should also specifically look for harms related to each on the interventions. Specifically, what would be the net effect of withholding long-term immune modulators, particularly patients' health status prior to surgery. The normothermia recommendation is no longer supported by current evidence,[90] but apart from the costs there

is seemingly little downside to providing this care given its likely benefit for patient thermal comfort perioperatively.

Digital health and registry-based trials

Digital health technologies have greatly simplified data collection and support decentralised studies.[101] These typically support disease and surgical registries that record extensive baseline, process and outcome data in real-world healthcare settings, offering the potential for registry-nested clinical trials.[6] It is an obvious appealing option to integrate these aspects into a perioperative platform, as has been done in related disciplines,[17-19] further maximising efficiencies and reduces the cost of clinical trials. Existing[102, 103] and future[104] perioperative quality registries are an appealing resource for this.

Sources of funding

The resources and time required to set up a platform trial are considerable but the overall costs are less than that required for a traditional series of conventional clinical trials, each addressing one clinical question.[105] Of course, once established, the return on investment of a platform trial will be much greater.

Very few national medical research funding agencies have systems in place to fund an ongoing platform trial. Funding for the UK's RECOVERY trial was to be stopped in October, 2022.[106] Some see the potential and value so may fund the set up costs and initial infrastructure, but still expect the coordinating team to demonstrate a capacity to gain funding for future treatment groups added into the platform.

Although several anaesthesia-perioperative medicine clinical trial networks have been highly successful in gaining national funding for their conventional clinical trials, new strategies are needed if platforms are to be successful. Multinational collaboration is essential, and multiple sources of funding most likely.

Conclusions

There are excellent opportunities for anaesthetists to establish platform trials in perioperative medicine. Platform trials are highly efficient, with the potential to provide quicker answers to important clinical questions that lead to improved patient care. Platform trials do however, introduce additional complexities requiring specific expertise and planning. Extensive simulations to evaluate different design options can be time consuming at the planning stage. Operational aspects linked to the different adaptations can be challenging and anticipation and careful scheduling are paramount. Funding and governance are more complicated given the evolutive nature of such trials. Collaboration and broad discussions among various stakeholders are essential to the success of platform trials.

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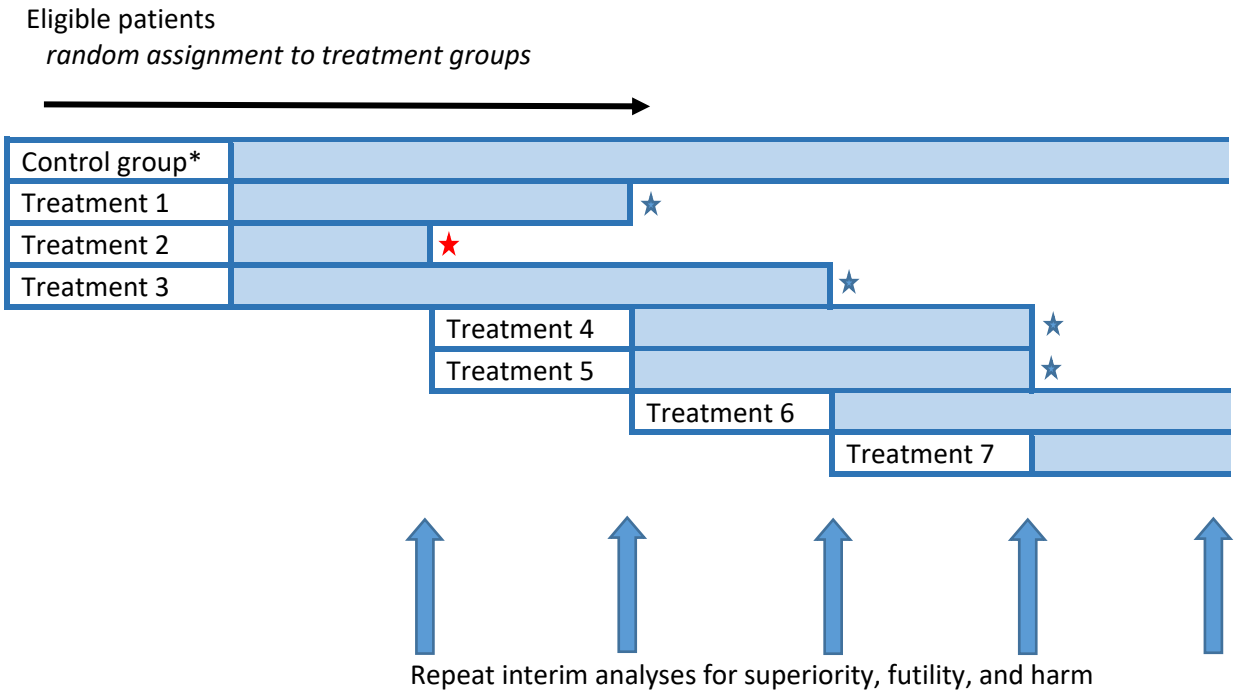
Figure 1. A single domain platform trial comparing 3 treatments (1 - 3) versus control, adding in 4 subsequent treatments (4 - 7), with assignment to a total of 5 treatments stopped during the life cycle of the platform.



★ Assignment to treatment group stopped after demonstrating superiority
★ Assignment to treatment group stopped after demonstrating harm

*The control group may include the entire control cohort across the lifecycle of the trial (both "nonconcurrent" and "concurrent" control groups) or be a subset that was enrolled and randomised in the same time period as the particular treatment being evaluated ("concurrent control group").

Figure 2. Potential prophylaxis strategies for postoperative delirium and other perioperative neurocognitive disorders.

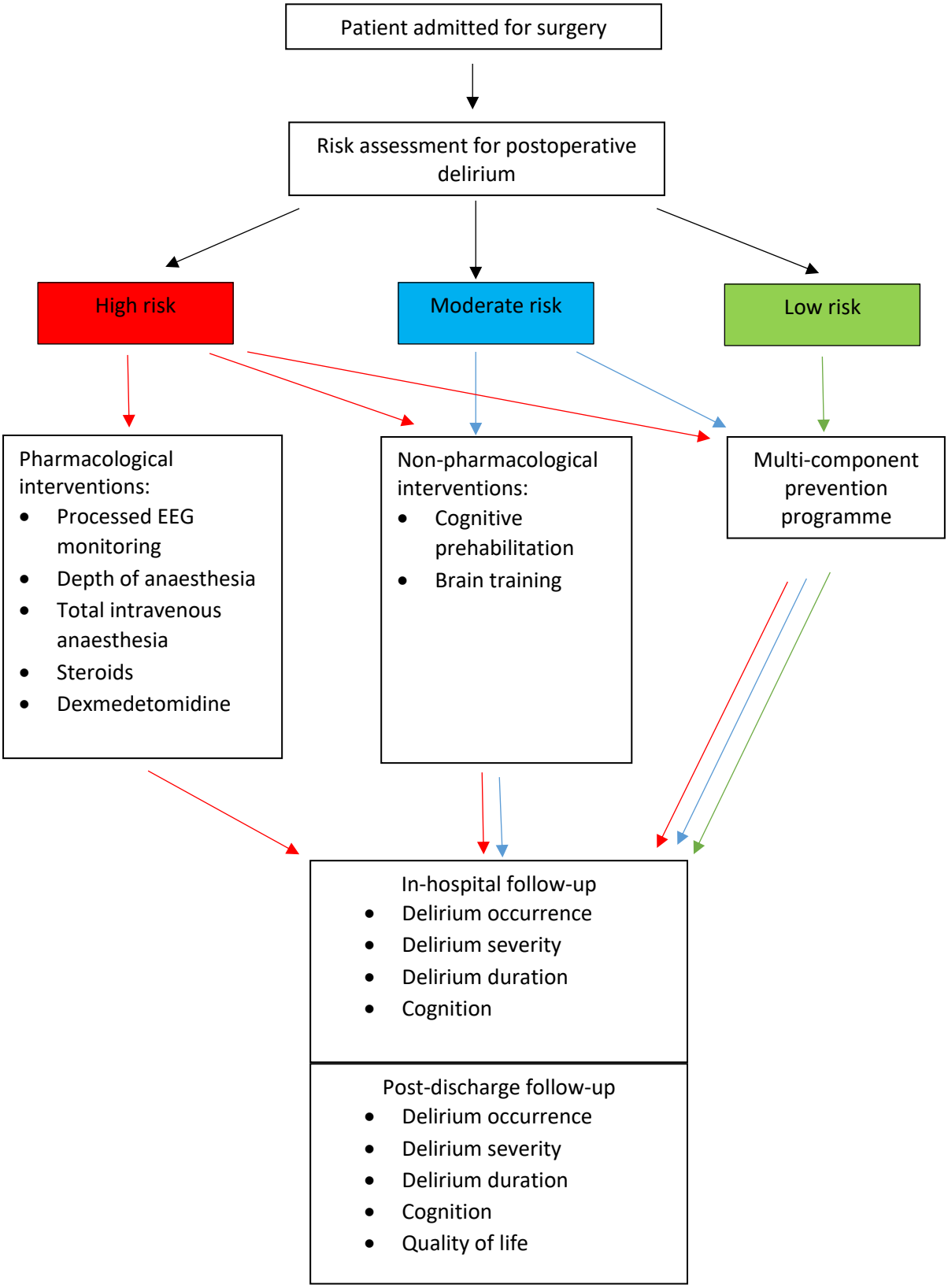


Table 1. Examples of potential platform trials in anaesthesia and perioperative medicine.

Perioperative complications/challenges
Delirium
Respiratory complications
Surgical site infection
Enhanced recovery care bundle
Myocardial injury
Cancer recurrence
Pain relief in labour

Types of surgery
Knee arthroplasty
Cardiac surgery
Caesarean section
Emergency laparotomy

Table 2. WHO surgical site infection guidelines: recommended processes during anaesthesia/perioperative care.

Process	Recommendation	Intervention	Strength of evidence	No. in MA	Potential Harms	OR (95% CI)	Systematic review: Reference
Immunosuppressive drugs	Do not discontinue immunosuppressive medication prior to surgery		Conditional: very low quality	249	Exacerbate underlying disease state		Web appendix 12 *PADDI trial results not considered*
Timing of antibiotic prophylaxis*	Within 120 minutes before incision	Antibiotic prophylaxis	Strong: moderate quality	No RCTs	Increased infections 2^{O} to low antibiotic concentration	<120 vs.>120 5.26 (3.3-8.4) Pre vs post incision 1.9 (1.05-3.4)	Web appendix 5 *Based only on observational studies*
Oxygenation Also recommended by NICE, CDC, SCIP	For adults undergoing general anaesthesia with tracheal intubation use 80% oxygen	80% inspired fraction of oxygen	Conditional: moderate quality	5976	Atelectasis, loss of lung volume**	80% vs. 30% *Intubated only* 0.80 (0.64-0.99)	Br J Anesth 2019: 122: 289
Normothermia Also recommended by NICE, SCIP, CDC	Use warming devices in the operating room and during the surgical procedure	Maintain core temp >36 degrees	Conditional: moderate quality	5058	Forced air warming increases laminar flow of particles	0.98 (0.83-1.25)	Web appendix 14 Reassessed after recent PROTECT study
Glucose control (NICE, CDC, SCIP have differing targets)	Intensive perioperative blood glucose control (both diabetic and non-diabetic adult patients)	No specific target blood glucose (150 mg/dl is the most studies target)	Conditional: low quality	2836	Unrecognised hypo-glycaemia	0.43 (0.29-0.63)	Br J Surg 2017; 104: e95–e105 All studies conducted in ICU setting
Goal Directed Fluid Therapy (GDFT)	GDFT is recommended intraoperatively to reduce the risk of SSI.		Conditional: very low to low quality	2830	Central venous	GDFT vs SOC 0.53 (0.35-0.88)	Web appendix 16

Also Recommended by NICE					catheter complications	Restrictive vs. liberal fluids 0.73 (0.41-1.28)	Did not include RELIEF or OPTIMIZE ll trials

WHO = World Health Organization; NICE = National Institute of Health and Care Excellence; CDC =Centers for Disease Control and Prevention; SCIP = Surgical Care Improvement Project: SOC = standard of care
MA = meta-analysis
*the recommendations from NICE is < 60 minutes, with adjustment for tourniquet
**a meta-analysis of increased oxygen fraction could not identify any harms