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CLINICAL TRIALS

Campaign strategy and tactics for clinical trials in surgical oncology

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The strategic planning of the campaign against cancer and the employment of clinical trials on a national and supranational basis could be improved. Lessons and principles derived from other spheres of ordered activity might be usefully applied to the realm of clinical trials. Principles taught by military strategists may find practical applications in the development and prosecution of successful clinical trials of cancer therapy. In this paper we reflect upon the parallels and divergences between the principles of campaign strategy needed for the successful prosecution of military objectives and the efficient and effective prosecution of major clinical trials.

Key words: **strategy; tactics; clinical trials; surgical oncology.**

Therefore, even when the likelihood of success is against us, we must not think of our undertaking as unreasonable or impossible, for it is always reasonable . . . if we make the best use of the few means at our disposal.

Pursue one great decisive aim with force and determination.

Carl von Clausewitz (1780–1831)
The Principles of War.[W1]

Introduction

In the war against aggressive cancer, we have neither achieved strategic ascendancy nor won many tactical battles in recent years. The clinical trial is an important weapon in our armoury and yet it is rarely wielded to best effect. The low global entry rate of patients into clinical trials testifies to the inadequacies in our present systems, such that opportunities for therapeutic progress are lost or delayed. Many other trials are initiated but not seen through to completion or publication. The problems of organization of large resources of personnel and material to complete complex tasks akin to clinical trials arise in many spheres of human endeavour. These include businesses, civil engineering projects and military operations. Lessons for clinical trials may be learned from the rules and solutions adopted by such organizations.

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Doctrine is the intellectual framework of knowledge and principles with which a complex problem such as a military campaign or a large clinical trial can be addressed. Many great military doctrinal thinkers and commanders have been produced in the Western world over the centuries. Carl von Clausewitz (1780–1831), a Prussian Army officer and military tutor to Wilhelm IV, has had an enormous influence on 20th century warfare. His pamphlet *The Principles of War* and his later book *On War* adopted the terminology of Newtonian mechanics, with concepts such as the centre of gravity, the concentration of force, the maintenance of momentum and economy of effort, to create and systematize a military doctrinal framework which has stood the test of time.[1,2,W1] Clausewitz also taught the importance of setting objectives in the context of the overall political framework.

We may consider to what extent there are parallels between the problems faced by military planners and by clinical trials planners and the lessons that the latter may draw from the professional doctrines of the former. It may be possible to improve the formulation and execution of effective clinical trials by the systematic adoption of a number of key Clausewitzian principles. These address the selection of the aim; the strategic and tactical planning, the optimum use of finite resources, and the mechanisms put in place to maintain the aim; so as to achieve the aim.

The strategic perspective

Strategic planning addresses the 'grand design' of a campaign and its overall objectives. Strategic planning is

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necessary to improve both the delivery of surgical oncology services and cancer research in Europe. Without strategic direction, resources will be misdirected, maldeployed and wasted. Strategic direction in health-care provision is a political imperative and much direction is imposed by governments, which control the resources. Strategically directed programmes may be less apparent in the disciplines of oncology than in health prevention and world-wide vaccination programmes. Political direction may engage statutory, financial or contractual methods to supplement persuasion in order to achieve the strategic objectives. It can also help to avoid duplication or conflict for patients and resources.

The strategic aim in surgical oncology may be to prevent, screen for or cure a particular class of cancer. We may aim to restore to patients affected by a certain tumour the same life expectancy as a matched cohort of unaffected individuals. We may aim to achieve the goal by national or international cooperation. However, cancer strategy is usually coordinated at a national rather than an international political level. In the UK, examples of successful political strategic direction of cancer services include the current national programme to consolidate cancer services around regional centres of excellence, and the National Breast Screening Programme. The UK Coordinating Committee for Cancer Research (UKCCCR) plays an important strategic role in the planning of national clinical trials.

Other bodies also confer strategic perspective within Europe, and within the field of cancer research. These include the European Organisation for Research and Treatment of Cancer (EORTC) and the International Union Against Cancer (UICC). Other professional bodies which can confer strategic direction on a programme by virtue of the scale of resources which they can bring to bear on a problem include the National Institute of Health (NIH) in the USA, and the World Health Organisation (WHO). One example of a major international strategic research programme is the Human Genome Project, the plan to improve the understanding of the cell and molecular biology of cancer and of the human genome. This exemplifies successful international strategic vision and cooperation.

Despite the existence of many bodies currently overseeing clinical trials in Europe, we must consider whether the planning of trials, the clarity of objectives and the persuasion of the large rank and file of surgical oncologists could be improved.

The tactical perspective and the clinical trial

Tactical objectives are components of the overall strategic plan and are subsidiary to the grand design. In clinical-trial terms, they may be considered to be the focus of specific therapeutic questions for given tumour types. These questions may be directed, for example, to the search for better surgical techniques or for better adjuvant chemotherapy and radiotherapy techniques. Tactical direction of specific trials and research programmes devolves to a variety of local, regional, national or supranational administrative bodies. These include charities, for example the Cancer Research Campaign in the UK, professional groupings such as the UKCCCR, and affiliated government agencies, such as the British Medical Research Council.

Should central planning or serendipity be the order of the day? The extent to which clinical trials should be ordered as a part of a centrally planned 'grand design' is open to debate. It might be argued that there need be no grand administrative design for the international research effort, on the basis that no one individual or committee can have the wisdom to conceive, plan and direct a strategic campaign appropriately. Indeed, as in command economies, central direction may stifle cooperation and participation and impair the emergence of ideas and momentum for new trials. Instead, opportunities and solutions should be allowed to emerge through decentralization and competition in an intellectual 'free market'.

Selection of the aim

The foundation of any successful military campaign is a clear and unambiguous statement of aim. Similarly, successful science and clinical trials mandate a clear hypothesis.[3] This self-evident truth can be overlooked. Specification of the aim demands intellectual discipline and a clear appraisal of all pertinent factors. This process will specify the fundamental operational objective. In a clinical trial, the aim must be sufficiently persuasive to clinicians to secure their active cooperation. Thus, it must be founded on a body of evidence or argument which is acceptable to and agreed by the participants. Selection of the primary aim of a clinical trial must take into account the many factors which affect its prosecution. There may be several courses of action open to the trials planner.

The formulation of the primary scientific aim of the trial should not be confused with the desire to secure recruitment to the trial. Where trials are formulated to maximize widespread participation, clinicians may be allowed considerable latitude in entry criteria. This risks blurring the clarity of the aim, obscuring the hypothesis, and impairing rather than facilitating prosecution of the objectives.

The issues of 'certainty' and 'uncertainty' of the participating clinicians at the design stage and in specifying the inclusion criteria for a trial are of considerable interest. The use of a clinical trial may be likened to resolving the 'fog of war'. In other words, the clinician wishes to find a clear answer to his or her problem within a mass of (future) clinical case data. Descriptive trials offer a very clear definition of patient categories, based upon prior certainty. This limits their general applicability, but they have value in the generation and testing of hypotheses, and for pilot and feasibility studies.

Conversely, pragmatic studies are founded in uncertainty, in that they represent the broad range of uncertainty among the clinical participants about a problem in the real world. They find general applicability and are thus of particular value in the determination of strategic direction for treatment policy. Two recent examples illustrate the value of the pragmatic study. Firstly, in a carotid endarterectomy study, it was possible to identify patterns of treatment outcome linked to degrees of stenosis which would not

have been apparent if a descriptive trial with an arbitrary randomization level had been formulated at the outset.[4] Secondly, the determination of the optimum duration for tamoxifen treatment may be established by inspection of data from a number of treatment studies, including the ATLAS and aTTom trials, for which outcomes have yet to be published.

Taken to the extreme, the pragmatic approach would allow us to examine all clinical data generated by all cancer treatments and patient episodes in the real world, just as the commander would like to know the precise dispositions of all forces on the battlefield at all times. We would then sift the effective from the ineffective treatment profiles and concentrate further specific resources on the most promising therapeutic strategies. Indeed, with the Internet resources now available, we can conceive of a time when such an approach could become attainable within a realistic frame of cost and clinical effort using standard (anonymized) data entry sets in all cancer centres. However, even in this model, we may not be able to exclude the possibility of treatment bias or to guarantee the accurate matching of cases with given prognostic variables.

One interesting example of how such a 'community' database might work is the PACE (population adjusted clinical epidemiology) strategy adopted by haematologists in the northern UK for the study of haematological cancers over a wide area. This provides a broad population-based context for study, which overcomes many of the handicaps of clinical trials.[5]

Subsidiary aims

In addition to the primary objective, there may be subsidiary objectives. Subsidiary aims should not distract from the primary focus of effort, or else effort, resources and recruitment will be dissipated in the confusion of aims. The problem of dissipation of effort through multiplication in the aims is faced in multifactorial trials. This may occur where there is a 'no treatment' arm and where one or other element of the study is emotively and subjectively more attractive or unattractive to participating clinicians and patients than the other, thus discouraging or slanting trial recruitment.

Economy of effort and concentration of available resources are important related principles of planning of military operations and clinical trials. The large clinical trial will consume considerable human and material resources. These must be effectively and efficiently conserved, focused and used to maximum effect to achieve the aim. Before any significant resources are committed to the task, it is essential to undertake a thorough 'analysis' of the 'mission'. The process of planning addresses the optimum use of resources to achieve the aim. All conceivable options should be considered and analysed exhaustively in an exercise known as an 'appreciation'.

Factors to take into account may include the time available for completion of a trial, the availability of administrative resources and local, regional, national and international geographical and socio-economic factors. Even a seemingly simple objective for a clinical trial can create a large number of options. For example, in order to recruit a given number of patients, effort and resources may be focused on a small number of hospitals over a longer time scale or on a large number of hospitals over a short period. Each choice offers advantages and disadvantages.

Time as a planning factor

Time is a key factor to be addressed at the planning stage. The time allocated to the project should be as short as possible, to maintain interest and momentum, and to avoid pre-emption of the trial by other studies. This creates a tension between the optimum duration of the study and the optimum number of participating centres in order to accrue the maximum number of cases in the time available. To motivate participants and to assess progress, realistic interim targets should be set. In military terminology, these objectives are known as 'phase lines'. In a clinical trial, a phase line might be a date for numbers of cases accrued.

Geography as a planning factor

Geography affects communications, the 'command and control' of a trial, and the recruitment base, and is thus a key factor in planning. There are a number of choices as to where the clinical research should be undertaken. It may be focused at the local, regional, national or supranational level. The known case load of individual surgical units and their track records in trials participation will have an important bearing at the planning stage and the better the information available to the planners, the more realistic the planning. Computer modelling to address 'what-if' scenarios has become an important feature of advance planning for military operations and we might consider the value of spreadsheet modelling at the planning stage of clinical trials.

Lines of communication

The length of the line of communication has a significant influence on the logistics, economy of effort, time and hence the outcome of a study, as for a military campaign. The local unit, for example an individual hospital, town or city, specialist referral centre or health authority boundary, has the shortest lines of communication. It can take advantage of the skills and enthusiasm of small groups of individuals, with the least bureaucratic delay. The effectiveness of a local study may be limited by clinical, financial and administrative resources.

Studies conducted within regions of one country, for example counties, provinces, or Lande, also benefit from short lines of communication, but have greater clinical resources. They can take advantage of a shared professional culture, common language and a local identity to maintain support and momentum.

National studies also have the advantage of a shared professional culture and a common language, as well as manageable lines of communication. There are also a number of national bodies within Europe for the organization of cancer trials. These include, in Britain, the UKCCCR, various charities, the Medical Research Council, and the British National Health Service (NHS) Directorates of Research and Development.

Multinational studies possess the advantages of large clinical and financial resources. They may involve large pharmaceutical companies and international bodies such as the World Health Organisation (WHO). Problems with multinational studies include language barriers, complex lines of communication, and differences in professional culture. There is also a risk in the formulation of international collaborations, that the primary scientific aim of the study will become subsumed in a political exercise in the promotion of European cooperation.

Modern electronic communications, e-mail and conferencing systems have substantially reduced the difficulties in administration imposed by distance, such that language rather than distance is probably now the most serious handicap to a freer exchange of associations. Even this is becoming less of a problem as English becomes the *lingua franca* of scientific exchange.

Logistics

Good logistics determine the success or failure of any military enterprise. The planning and organization of large trials mandates professionalism, resources and a body of administrative expertise. Logistic challenges for trials include the documentation, the collection and dissemination of data, and the coordination of triallists. The complexities and demands of multicentre trials mandate central administrative bodies to maintain and disseminate expertise, rather than *ad hoc* organizations for the administration of individual trials.

Table 1. The 'principles of war' for clinical trials

1. Some useful doctrinal principles (after Clausewitz)
- Identification of the 'centre of gravity' of the problem
- Use economy of effort to achieve the aim
- Concentrate forces (resources) to achieve the aim
- Maintain momentum once operation is under way

2. Processes in the implementation of Doctrine
- Selection of the aim
- The strategic aim
  - set at national or international political level
  - or by established cancer bodies, e.g. UICC, EORTC, NIH
- The tactical aim (the clinical trial) may include
  - effective screening programmes
  - the determination of optimal surgical strategies
  - the development of effective adjuvant therapies
- Achievement of the aim
- The appreciation and mission analysis
  - The appreciation of positive and negative factors
  - Factors include
    - the optimization of patient recruitment
    - the timescale in which to achieve objective
  - Potential problems include
    - loss of key skills or personnel
    - geographical, funding and recruitment constraints
- The maintenance and prosecution of the aim
- Factors include
  - optimization of the leadership function
  - the maintenance of morale among contributors
  - the efficient administration of the trial
  - efficient communication, cooperation and training of participants

Within each trial, hierarchies of leadership and administration must also exist. Hierarchical tasks may include a clinical trials office to ensure efficient administration and logistics and an independent statistical team to plan and supervise the data analysis. These services are often available to individual trials from established specialist bodies and trials administration offices.

Battle space

The US military has, in recent years, adopted a command and control concept known as *battle space*.[W2] The use of satellites, powerful remote sensors, precisely targeted weaponry and computerized communications has added a third dimension and a compression of time to the theatre of operations. Huge volumes of information can be abstracted from many sources to present a comprehensive picture of operations to planners.

This capacity for total envelopment of the strategic problem finds conceptual applications in the world of cancer. Cancer research and treatment are highly fragmented on a world-wide basis and may contain many inefficiencies. The lack of coordination of many dimensions of data, from basic research to clinical treatment in many subdisciplines of cancer practice, may be concealing important signals. The sheer volume of publications, meetings and clinical activity prevents any one individual from seeing a complete picture, such that basic researchers and clinical practitioners are often isolated from each other. Can we find lessons and algorithms within the computerized technology of battle space management which are appropriate for the coordination of cancer research?

Maintenance of the aim

A critical challenge with military campaigns and clinical trials is to ensure maintenance of the original aim once the initial onslaught or enthusiasm has dissipated. Loss of momentum can lead to failure of a well-conceived and well-planned project. It may be brought about by a variety of factors. Unforeseen problems may arise. In military parlance this produces 'friction', or the 'fog of war'.

In clinical trials, no campaign runs entirely to plan, and a fog may descend. Failure to conclude or publish a clinical trial wastes resources and delays the introduction of better clinical practices. Clinical trials may meet all sorts of obstacles, ranging from insufficient recruitment to adverse events and media publicity, or competition for patients from other trials. There may be budgetary problems, a loss of key expertise or personnel, ethical committee procedures, or unsatisfactory case accrual rates. New scientific information or concurrent clinical trials may distract participants. Boredom may supervene and the interest and support of contributors may be lost.

The maintenance of morale

Good morale among participants is crucial to the maintenance of the aim. Success in any complex human endeavour is determined as much by moral as by material

resources. The 'will to win' is necessary for the successful prosecution of a clinical trial, and stems from good leadership and planning, and a belief in the validity of the objectives. It allows difficulties to be overcome and complex tasks to be achieved. Conversely, poor morale and dissaffection among trial participants will soon slow recruitment and hamper the prosecution of the aim.

Leadership

The act of bringing together a large number of individuals and material resources to achieve a desired goal requires leadership and administrative skills. The issue of leadership is a particular challenge in the clinical world. Successful endeavours are often associated with individual leaders, but clinicians are traditionally averse to the cult of the individual, *primus inter pares*. It is nevertheless sensible to invest every trial with an identifiable, respected, competent and committed leadership. Good personal leadership may be expected to ensure completion of the task and will motivate the participants during the progress of the trial. Human factors and the motivation of individual clinicians are particularly challenging in a large clinical trial, where the planner cannot command events as in a military hierarchy. In the absence of the profit motive available to business planners, or the stick of military discipline, clinical trials leaders must harness less tangible and more altruistic human motivations. However, during the course of the 'campaign', the ambitions of the individuals will need to be subordinated to the group objectives, and professional discipline and cohesion is as important as in a military campaign.

It is rare for individual leaders to be identified publicly with clinical trials. The Committee of experts is the usual managerial focus for a clinical trial. This may be convened as a result of political direction, by an international body such as the EORTC, by a national statutory body such as the UK Medical Research Council, by a charitable body, or simply by a convergence of like-minded individuals.

Nevertheless, leadership by committee rarely proves inspirational to the human spirit in any field of human endeavour. It is reasonable to consider how and whether the leadership function of large clinical trials should be personalized and invested more clearly in individuals on a full-time, salaried basis. Many trials are run at present by dedicated individuals with other clinical and administrative commitments.

Communications

Good leadership mandates good bidirectional communications with the 'forces under command'. These communications achieve two purposes within the organization of trials. Firstly, they ensure efficient administration, and secondly, they improve motivation and cohesion for participants who may be geographically isolated from other participants. Good communications may include use of telecommunications, regular newsletters, or regional and national meetings. Good leadership also requires regular personal contact and face-to-face communication. Visits to participating units benefit morale, encourage participation and allow the assessment of problems which may be hindering recruitment. An annual national review meeting for triallists is another option.

Cooperation

This 'principle of war' encompasses team spirit, the coordination of resources, and goodwill. Cooperation leads to efficient use of resources, economy of effort, and good morale. Each plan must take into account the available resources and the factors which will facilitate the aim, for example, publicity and support from the local or national media to improve trial recruitment or available funds. Scientific and laboratory facilities may be available in other institutions.

Better cooperation has been an important and worthy objective of many political, military, health and economic programmes in Europe for 50 years, and also of heath issues. International cooperation in surgical oncology is impaired by language, geography and different professional cultures, each of which must be addressed or circumvented if cooperative pan-European trials are to succeed. New developments in technology, and particularly the Internet, may help produce a framework upon which effective cooperation can be built.[6]

Training

No military campaign succeeds without training and rehearsal. In order to improve professional participation in clinical trials, it may be necessary to raise the awareness of the importance of trials early in medical training. The principles of clinical trials could be better incorporated in the undergraduate curriculum. Modern technology can aid the instruction process. For example, the clinical trial can be modelled as an electronic 'game' for optimum planning and for self-learning. Spreadsheets and project management software can be used to improve the understanding and management of trials. Perhaps we have a need for national and international training programmes and centres for the dissemination of 'operational level' skills for the formulation and management of clinical trials.

The foot soldiers: the triallists or the trialled?

Every campaign has its foot soldiers, and we may debate whether the foot soldiers of clinical trials are the many clinicians and nurses who do the legwork, or the patients who are in the firing line and at true physical risk.

Orders or informed consent?

The military commander has the sanction of orders and discipline to ensure the necessary responses from the soldiery. The clinical triallist must fall back upon persuasion and informed consent. There is a clear conflict between the accepted right to autonomy and personal choice in modern Western liberal democratic thought, and the need for blinding of choice in ethical clinical trials. This poses problems and is a necessary deficiency of the trials process. We may determine a strategy for a clinical trial which is intellectually unassailable and which is demonstrably in the

best long-term interests of the community, but which falls down because patients are not obliged to participate. Consent may be withheld because of lack of understanding by the patient, or because of misperception such as that any medication must be better than no medication, or because of ill-conceived media comment or speculation.

Mass mobilization

The success of clinical trials ultimately depends upon the willing participation of, and indeed the pressure to participate upon, the general public. We need to remedy the problems for recruitment with a continuing campaign of public education. This may be coordinated at a national or an international level. For example, in the UK, the Consumers Advisory Group has been co-opted to help mobilize public opinion in the support of clinical trials.[7,8]

The responsibility for success in the mass mobilization of public opinion ultimately rests with the individual clinician, who should use every local opportunity to educate other professionals, students, patients and the media. The mass communications media are often unable to convey the complex arguments deployed in clinical trials in a way which will hold the attention of their audience and it is our responsibility to simplify and clarify the debate.

Funding

There are, sadly, few parallels to be drawn between the scale of clinical trials funding and a defence budget. It is a source for regret that clinical trials work does not generally command a greater priority for funds, although in recent years a large sum of money (some US$ 200 million) was curiously made available in the US defence budget to advance breast-cancer research. Conversely, we may reflect upon the civilian medical gains from military technology transfer. One oncological example in the past century is the emergence of the entire science of cytotoxic chemotherapy from the use of nitrogen mustard incapacitating agents. The immense benefits which seem likely to accrue from the Internet owe their existence to the US Department of Defence's computer network, designed to withstand nuclear conflict.

Concluding comments

The effective prosecution of clinical trials can draw inspiration from organizational experience in many other fields of human endeavour. There are many current and past examples of excellence in the formulation, pursuit and completion of clinical trials. However, the failure of other trials, and the poor utilization of the vast national, European and world-wide resources of clinical cases in trials testifies to the need for a better training and awareness throughout the clinical hierarchy. We do not yet conduct and pursue clinical trials as well as we might, and the lessons of other organizations may help us to do better. Progress in the management of cancer may demand as great and as focused a strategic national and international effort as in any major military campaign. It is possible that many trials would benefit from a disciplined application of the principles outlined. Old ideas in new contexts may be useful weapons in the struggle against a resilient adversary.

The people's health is the concern of the people themselves. They must want health, they must struggle for it and plan for it. Physicians are merely experts whose advice is sought in drawing up plans and whose cooperation is needed in carrying them out . . . The war against disease and for health cannot be fought by physicians alone. It is a people's war for which the entire population must be mobilised permanently. (Henry E. Sigerist, quoted in[9]).

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