How to undertake research in wound healing

In planning a wound healing research project the complexities of human physiology, variations among individuals and the systemic response of the body to an insult (trauma) have to be taken into account. Various aspects need to be considered, including proposing a hypothesis (research question), choosing an appropriate study design, obtaining ethical approval, calculating sample size, appreciating inherent and essential ethical issues, and addressing the source of funding. Thereafter, emphasis should shift to how to report research findings as a means for dispersal of knowledge. This article provides an overview of the research process.

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The importance of research in wound healing cannot be overstated. Advances in wound management in the past two decades continue to dictate modern practice; ranging from intermittent pneumatic compression (IPC) as an effective means for managing a variety of non-healing chronic wounds recalcitrant to other modalities of treatment (Enoch et al, 2006), through to the use of hyperbaric oxygen to overcome the effect of hypoxia seen in non-healing wounds (Thackham et al, 2008). In addition, significant advances in gene therapy, especially knowledge of specific growth factors, receptors, adhesion molecules and inhibitors of proteases (Branski et al, 2009) have further aided the management of chronic wound care provided by healthcare professionals.

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Research in wound healing

Wounds may arise from a variety of aetiologies such as peripheral arterial disease, venous hypertension, neuropathy (e.g. diabetes mellitus), pressure (in patients with neuropathy or decreased mobility), vasculitis and burns. A large proportion of acute wounds heal with appropriate management, but some wounds fail to heal and proceed to becoming chronic, non-healing wounds. Although research in the management of acute wounds such as burns is certainly worthy of focus, chronic wounds — due to their significant implications for the patient, hospital and community — deserve more attention.

A 'completely healed wound' can be defined as one that has returned to its normal anatomic structure, function and appearance within a reasonable period of time (normally in about four to six weeks) (Enoch and Price, 2004). Any wound that has not reached the above state would be considered a chronic, non-healing wound. The problem may lie in disruption at one or more points in the phases of wound healing (haemostasis, inflammation, proliferation, or remodelling). The inflammatory response familiar to acute wound healing is predictably altered in chronic wounds. On a molecular level, an alternation in the balance between various cytokines, growth factors, protease activity, matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) is observed in chronic wounds (Cook et al, 2000). In addition, alteration in the morphology and proliferation rate of fibroblasts, keratinocyte activity, and accumulation of oxygen derived free radicals (Clark, 1996) and necrotic tissue (Clark et al, 1982; Enoch and Leaper, 2008) all play a role in inhibiting wound healing.

There is a propensity for ulcers to affect the lower limb and the estimated prevalence of active leg ulceration in Europe is about 0.1–0.3% (Cornwall and Lewis, 1983; Callam et al, 1985; Nelzen et al, 1996). Moreover, chronic wound ulceration is a global issue, for instance, it affects 1% of the general population of the UK and 3.5% of those people aged over 65 (Hess and Kirsner, 2003).

Importance of a good research question

Investigation regarding wound therapy has frequently been the subject of scientific literary review. This trend continues today, most recently in the *Lancet* where Ferguson et al (2009) report the role of transforming growth factor beta3 (TGFβ3) in the regeneration of healing wounds and minimising scarring.

When undertaking effective research, a good research question (hypothesis) is an essential initial requirement. The research question must be simple, focused and clear. It might be useful to have a session of brainstorming between the researchers during the early design process. The research question may arise from a specific problem, clinical or investigative, that has been previously identified. It is also necessary to ascertain the outcome measure (endpoint) of the study and the potential implications of the study. Another prerequisite is to ensure adequacy of resources (money, materials, patients and staff), and this is often aided by performing a pilot study. A thorough literature search should then be performed and the study designed.

Study design considerations

A wide range of clinical epidemiological methods or trial designs are available for evaluating wound healing: case studies, clinical surveys, cohort studies, case-control studies, intervention trials, randomised controlled trials (RCTs) and cross-over trials. The essential purpose in all designs must be to reduce all types of bias and in many instances this can be established via stratified randomisation, be it in important covariates, such as state of wound bed, wound size and treatment duration.

Case studies

This type of study might be sufficient for evaluating a new device or dressing; for instance, a novel topical agent for treating burns. This could be carried out to test the efficacy and other unexpected possible side-effects of a treatment before planning a large trial. As such, this can be considered to be a pilot study. However, on their own they do not produce sufficient evidence to make firm conclusions and the level of evidence obtained from case studies is insufficient to change practice.

Clinical surveys

These are also called 'cross-sectional' studies, often using samples, and are designed to measure the prevalence, and more particularly to study the associations between health status and various (possibly causal) factors (e.g. association between spina bifida and pressure ulcerations). The information gained from clinical surveys could be used to plan further studies and thus again be used as a pilot study.

Cohort studies

By first surveying, and then following a sample (cohort) of people, it is possible to measure by how much the incidence of disease (condition) differs between those who are exposed to an intervention or not exposed to an intervention (measured at the time of survey), and those who are not exposed (not intervened) (e.g. selecting a population of interest, identifying people who had deep venous thrombosis [DVT] and following them up to find what proportion develop venous ulceration). In addition, the role of prophylactic graduated compression hosiery (stockings) could also be evaluated by this study design. This is a valuable and quite widely used design and it provides a measure of the strength of association. Though this design is less open to bias than case-control studies, patients need to be followed-up for longer periods of time, thus increasing the duration of the study and the cost. Difficulties in long-term follow-up, such as patients migrating to another geographical area and the researchers 'moving on without completing the study' should also be considered.

Case-control studies

In these studies, people with a disease or a condition (cases) and people without (controls) are investigated, essentially to find out whether 'exposure' to a factor of interest is greater among the cases than the controls (e.g. smoking and arterial ulceration). It is a focused research design that allows measurement of the strength of the association between a disease or condition and its possible cause, or factors (such as health interventions) that can afford protection. These studies are also ideally suited to investigate rare outcomes, since by focusing on the cases and a suitable control group, it becomes necessary to gather data on only a relatively small number of individuals.

Intervention trials

By taking a sample of people and intervening among some but not others, it is possible to assess how much the level of health or incidence of disease has been altered by the intervention (e.g. to evaluate the effect of a new silver-containing dressing in expediting wound healing); randomly selected patients are intervened (given silver-containing dressings) to find if this form of treatment is effective and superior as compared with non-silver dressings. Evidence from such trials is powerful, especially if randomised, controlled and blinded. Since the investigator has much more control over the factor he/she wishes to test, in many respects it is an excellent research design. However, there are many situations where this approach is impractical and/or unethical (e.g. giving no pressure relief for patients at risk of pressure ulceration).

Randomised controlled trials (RCTs)

These are widely acknowledged as a powerful research tool for evaluating health technologies and considered to provide Level 2 evidence (Level 1 evidence is from the results obtained from more than one RCT). Their principal strength is that they minimise bias. Protection from selection bias is provided by random allocation to alternative technologies and analyses based on the groups as allocated, thereby ensuring that the groups being compared differ only by chance. Ascertainment bias can be avoided by arranging that the outcome is assessed in ignorance of the treatment allocated. Co-intervention bias is minimised by blinding treatments (where possible) and by employing clearly described treatment policies, which should be identical for each group apart from the intervention under examination in the RCT.

Cross-over trials

This is a special type of RCT that uses subjects as their own controls and thereby reduces random error and the sample size required. During

the course of the trial, each subject crosses over from receiving one treatment to receiving the other. This strength has to be balanced against the problem of 'carry over' and order effects, so it can only be used in certain types of interventions. However, in a significant proportion of wound studies, the status of the wound and/or the wound bed at the start of the study is not the same 8–12 weeks later when the wound is exposed to the second form of treatment. In such instances, comparison between two forms of treatment might not be truly meaningful.

How to calculate sample sizes

Sample size calculation is a vital part of the planning of a trial, and, together with advice from a statistician, these measures can reduce the chances of obtaining erroneous results on completion of the study. In simple terms, if an appropriate *significance level* is not chosen or there are not enough patients/subjects in a particular study, the results obtained are often incorrect. The salient aspects of sample size calculations are discussed below.

When two treatments (e.g. different forms of non-adherent dressings) are compared in a randomised trial, it is possible that one treatment modality appears superior to the other, purely by chance. In such a situation, it would be a Type I error if it is concluded that one form of treatment is better than the other. The chance or probability of a Type I error is called the significance level of the test and is usually denoted by alpha (α). Typically, a significance level of 5% is chosen: the probability of a Type I error occurring is 5% or 0.05. In other words, the probability of a false-positive result, given no difference in effectiveness, is 5%; this is called the *'P value'*.

If in a similar trial, the results falsely suggest no difference between the two forms of treatment, when in fact one form of treatment was superior to the other, a Type II error occurs, i.e. the genuine difference in outcomes is not recognised as being real. The probability of a Type II error is denoted by beta (β). This will happen if the trial is too small relative to the amount of random error, so that when the hypothesis test is applied a non-significant result is obtained. The trial must therefore be designed to be large enough to avoid this mistake. This is described as ensuring that the study has enough 'statistical power'. The power is the probability that we reject the null hypothesis (tested using a chi-squared or a t-test) when it is in fact false (note that a Type I error occurs if the null hypothesis is rejected when it is in fact true). Since the probability of this error is β, the power of the study – which is the probability of avoiding this error – is $1-\beta$. Commonly, a power of 80% is chosen and therefore β, the probability of a Type II error occurring then is 20%. This probability can be calculated given the required P value (e.g. 0.05), the number of people on whom outcomes will be measured and the size of the effect sought (sometimes called δ). The number of patients who must be recruited and followed up can be calculated given the power (i.e. $1-\beta$), P value (e.g. 0.05) and δ.

Ethical approval

Any form of study that needs access to patients (questionnaire, investigation or treatment), patient records, or involves collecting patient data in any form needs approval from the appropriate ethics committee. This may be at the level of the NHS trust, the university, the Local Research Ethics Committee (LREC) or the Multicentre Research Ethics Committee, as in the case for large trials and those involving various centres/hospitals. No study should start without obtaining ethical approval. Common questions asked in the ethics approval form when seeking approval are shown in *Table 1*.

Ethics committees

Research proposals in the Western world are subject to rigorous scrutiny by ethical committees (independent bodies composed of medical, scientific and non-medical and non-scientific professionals, whose responsibility is to ensure the protection of the rights, safety and well-being of the human subjects involved in a particular clinical investigation). The objective of the ethics committees is to review and to act in agreement with good clinical practice so as to protect the rights of subjects, to ensure that any clinical investigation done is ethical and scientifically valid, and not at the expense of fellow human beings (Royal College of Physicians of England, 1996).

Ethical issues and dilemmas

It may be known from the outset that at least some of the participants in a given piece of research will not themselves benefit. Despite this predicament, healthcare professionals have an ethical responsibility to offer their patients the best available medical care and are expected to put the medical needs of their patients above all other considerations. According to the revised Declaration of Helsinki 12: 'Concern for the interests of the subject must always prevail over the interests of science and society'. In the context of a clinical trial, the clinician cannot be expected to compromise the well-being of that particular patient in favour of anonymous patients elsewhere. This seems generally to be taken to imply, for example, that when a patient takes part in a clinical trial, the treatment within that trial should be in his or her best interests. Such interests should never be compromised for the sake of those patients in the future who might benefit from the trial results.

Consent for research

Informed consent is a doctrine by which patients may protect themselves from unwanted interventions and take responsibility for shaping their lives as they see fit (Herbert, 1996). Consent is required by law and not to get consent is to violate the patient's moral right of respect for autonomy.

In wound care research, it is common for a significant proportion of patients to be elderly. Such patients may not be able to give informed consent as they do not fully understand the treatment options being put forward. Similarly, in certain instances, it might be necessary to undertake research in disabled patients and children. It is acceptable to undertake research

in these groups of patients provided the appropriate ethical guidelines are adhered to. In this regard, Article I.11 of the Declaration of Helsinki states, 'In the case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or where the subject is a minor (child), permission from the responsible relative replaces that of the subject in accordance with national legislation'. In addition, it states, 'whenever the minor (child) is in fact able to give informed consent, the minor's (child's) consent must be obtained in addition to the consent of the legal guardian' (World Medical Association, 1996).

Funding

Funding for research can be obtained from a variety of sources. For small to medium scale projects, the research and development directorate within the NHS or the university have a range of grants to help both new and established researchers initiate projects (e.g. pump priming grants and young researcher grants). Various organisations and charities such as the Medical Research Council, Wellcome Trust, National Institute of Health (US), British Association of Plastic, Reconstructive and Aesthetic Surgeons, Action Medical Research, Wound Healing Research Unit, Cancer Research UK, Royal College of Surgeons, Royal College of Physicians, Royal College of Nursing and The Healing Foundation offer a diverse range of fellowship programmes (salary for the researcher and consumables) and grants for medium to large scale projects. In addition, particularly in wound healing research, a substantial amount of funding is provided by the industries and commercial companies (Enoch et al, 2007). The relationship between academia and industry is well established, and a significant number of recent advances in wound healing have obtained fruition due to this partnership. Contract research, collaborative research and consultancy are the three major forms of collaboration between academia and industry in wound healing research.

Table 1

Examples of common questions asked in the ethics approval form

- What are the objectives of the dissertation or research project?
- Does the research involve NHS patients, resources or staff?
- Do you intend to collect primary data from human subjects or data that are identifiable with individuals?
- What is the purpose of the primary data?
- What is/are the survey population(s)?
- How big is the sample for each of the survey populations and how was this sample arrived at?
- How will respondents be selected and recruited?
- What steps are proposed to ensure that the requirements of informed consent will be met for those taking part in the research?
- How will data be collected from each of the sample groups?
- How will data be stored and what will happen to the data at the end of the research?
- How will confidentiality be assured for respondents?
- What steps are proposed to safeguard the anonymity of the respondents?

Academics benefit by receiving grants and financial support from industry to pursue research in their chosen field of interest. The industry also benefits since, in addition to their own research and development department, they utilise the skills of outstanding clinical researchers and academics within the 'scientific world' for the evaluation and also creation of novel drugs and devices. Most clinical trials that bring new drugs or devices for routine clinical use are financed by industry. However, notwithstanding the benefits of this symbiosis, their emerging relationship has been a subject of fierce debate in scientific, ethical and even political quarters.

Industry funding in research

Universities, teaching hospitals and individual researchers (from academia) are constantly attracting industry sponsorship for research, and the pharmaceutical industry has become the single largest funder of medical research in Canada, the UK and the US (Collier and Iheanacho, 2002). It has been estimated that the average cost of bringing a new drug to market in the US is about $500 million (Mathieu, 1999). Although precise figures are not available, the cost required to bring a medical device used in wound healing (such as a medication bandage to treat venous leg ulcers) into the market would not be very different.

Issues and conflicts of interest in academia–industry partnership

Historically, academic principles of education (research) without bias or prejudice, discovery driven by curiosity, and the ownership of intellectual property by its inventor are firmly embedded in our institutions and culture. This stands in contrast to the industrial sectors' primary goal of product development, marketing and profitability. They have different values and missions, working on dissimilar timescales under different management systems — thus, they do not make easy bedfellows. There are several areas where potential conflicts of interest arise in the academia–industry liaison.

These include ownership of intellectual property, data analysis, preparation of manuscript and publication of results (Blumenthal et al, 1997; Bodenheimer, 2000).

Furthermore, critics argue that the engagement of academic researchers in clinical research can be bartered and the outcome of research could be biased by academia–industry liaisons, whether individual or institutional, that eventually leads to the quality of the research being affected. It has been alleged that industries intrude with the academic freedom of the university laboratory by placing constraints on crucial issues such as unbiased data interpretation and conclusion of the study (Downie et al, 2002; Nathan et al, 2002; Tuech et al, 2005). The consequences might lead to delays in the publication of the results because of disputes fuelled by issues sometimes related to economics and the stock market rather than the scientific merit of the study.

Future of industry-funded research in wound healing

Translation of burgeoning scientific advances to clinical medicine remains a formidable challenge, not only because of intellectual and practical hurdles involved in implementing knowledge gained at the bench to a bedside setting, but also because of severe financial constraints in the academic sector. Although critics claim that the relationship between the industry and academia (investigator) might have been tainted by a commercial motive, it needs to be acknowledged and accepted that without profit, the industry will cease to invest in the healthcare sector, which will be severely detrimental for medical science. Thus, academia and industry are inextricably linked in the modern world and they would serve the public best if they go hand in hand (*Table 2*). Academic participation in drug-related science both spurs innovation and, through the disinterest and scepticism that are hallmarks of the academic mission, provides a check on the premature enthusiasm of industry. The alliance between academia and industry, despite the fierce debates and the inevitable tensions, is a valuable one that should be nurtured and perfected. Industry-sponsored research might be considered to be a double-edged sword, but, if wielded with care, is capable of attaining cutting edge advances in the field of wound care.

Documentation and confidentiality

Good clinical practice requirements are found in various documents governing medical devices and clinical investigation including the Regulations for Investigational Device Exemption published in 2009 (Food and Drug Administration [FDA], 2009). These requirements should be considered primarily as a set of management tools which ensure that data is correctly and properly recorded, and that the rights of patients are protected by independent overview. Proper documentation enables the sponsor and healthcare professional to monitor, and the assessor adequate means to assess, the verification of the manufacturers' claims of the devices' technical performance. Moreover, it ensures that a structured and disciplined approach is undertaken for the effective management and execution of clinical investigation, and for the reliability of the clinical data.

Confidentiality is also a vital part of the understanding on which the clinician-patient relationship is based, and is a central ethical pillar of clinical practice among all healthcare professionals. On the matter of attaining patient data from medical records for study purposes, appropriate patient consent should be sought and the confidentiality of patient information ensured. However, in certain types of studies (such as epidemiological studies and large retrospective reviews) involving the scrutiny of thousands of computerised records or patient notes, it may be impracticable to seek the permission of every patient and may even be unethical if it causes large number of unaffected individuals needless anxiety. To this end, guidance has been provided by the World Health Organization (WHO) and the Royal College of Physicians (RCP). According to WHO epidemiological guidelines (Council for International Organizations of Medical Sciences [CIOMS]/WHO, 1993), if individual consent is not obtained, 'an investigator who proposes not to seek informed consent has the obligation to explain to the ethical review committee how the study would be ethical in its absence'. However, the RCP (RCP, 1996) takes a different view: it advises that so long as the same strict code of confidentiality is observed when medical records are used for research purposes as in standard clinical practice, it may not always be necessary to ask the patient's permission first. It further says that ethical review is not essential if no patient contact is involved. Since the guidance varies from country to country and organisation to organisation, it is prudent to adhere to accepted local or national guidelines and also consult the ethical committee if need be. If in any doubt, err on the side of caution, i.e. obtain consent before accessing patient records.

Table 2
Role of industry in wound healing research

- Technological and therapeutic innovation
- Product development and refinement
- Safety evaluation
- Clinical evaluation, health economics
- Laboratory-based research
- Education of healthcare professionals

Reporting research findings

It is clearly important to report the findings of any research or a trial to the wider world and to the scientific community. This serves not only in disseminating knowledge, but also provides an opportunity for other professionals to critically analyse and scrutinise the findings, allowing theories to be challenged, and identify any pitfalls or omissions of the study. In addition, research findings can influence

decisions at many levels — individual patient care, practice guidelines, policy development, commissioning of health care, prevention and health promotion, education and clinical audit.

The usual medium of such dispersal of knowledge is via presentations in international and national scientific conferences or publication of the results in peer-reviewed journals. Needless to say, publication in journals is more significant since it reaches a wider audience, can be accessed globally, becomes embedded in the medical literature, thus providing reference for future work, and above all, is available for more intense examination and critical analysis by innumerable experts in that field.

Authorship

All persons designated as authors should qualify for authorship, and all those who do should be listed. Each author should have participated sufficiently to take public responsibility for appropriate portions of the content. One or more should take responsibility for the integrity of the work as a whole, from inception to published article. Multi-authored papers should be scrutinised by all those who contribute before being sent to the publisher, so that they are able to defend the final published article.

Integrity in publishing results

In the academic world, the pressure to conduct research and publish results within a short time span is considerable. In the race for promotion, tenure and recognition, academics frequently gauge their career progress against the length of their bibliography. Researchers and practitioners working in or associated with an academic environment, though acknowledging this fact, should always strive to maintain the highest standards while conducting and reporting their research findings — that is with utmost honesty, integrity, openness and accountability. It should be remembered that all science builds future work on the established base. Hence, the accuracy of such work could affect large sections of the human population, sometimes for generations.

Table 3

Future areas of interest in wound healing research

- Tissue engineering and tissue engineered skin substitutes
- Growth factors and cytokines
- Specific enzymatic inhibitors (e.g. protease inhibitors, inhibitors of neutrophil elastase activity)
- Modulation and modification of wound environment (e.g. modulation of neutrophils, inhibition of enzymes involved in generating reactive oxygen metabolites)
- Recombinant DNA technology
- Gene manipulation and gene therapy
- Stem cells
- Scarless wound healing
- Pathology and patient-driven therapeutics
- Health-related quality of life and health economics

Discussion

With rapidly advancing understanding in wound science and technology, medical research is poised to play an ever crucial role in modern life. The collaborative efforts of healthcare professionals, patients, public, ethics committees, and the government are essential to develop the high standards that are needed to conduct ethical research for the betterment of the human race.

With regard to how research should be undertaken, the authors would argue that the greatest emphasis should lie in the choice of the research question. Once identified, it should be evaluated on three important aspects:

- The potential implications of the study
- The type of study design required
- The resource implications.

In addition, clear and meticulous planning is vital before embarking on any study or trial, since many research projects are never completed. This can occur if the study was more difficult than anticipated or the researchers lacked the resources. Resource does not just refer to money, but to all the materials needed to complete the study, including patients, staff with appropriate skills and expertise, filing systems and computers. As well as planning, the components of a study should be tested before the research is begun in earnest. It is advisable to start the main study only when it has been piloted and found to work, or suitably modified if it has failed. The guiding rule is: 'Do not begin unless you are sure to finish'.

After the studies are completed, it is essential that the results are published. Unfortunately, the results of many good research projects are not published at all and can be seen languishing in the filing cabinets of laboratories and research units. The enthusiasm for a project can wear thin by the time it comes to writing reports, and it takes great effort and perseverance to see research through to publication. Therefore, during the planning stages, adequate time should be set aside to complete the data analysis, prepare the tables and graphs, and to write and revise the manuscript.

While it is essential for the research in wound care to benefit patients and society, there are also direct personal benefits to healthcare professionals

from an active involvement in research. This includes: validation of novel treatments and therapies; the potential to improve the nature and the quality of treatment provided; the opportunity to change the culture within which wound care is delivered by encouraging others to be interested in research; and the personal satisfaction of contributing to knowledge. Furthermore, it also stimulates reading of the literature and honing critical appraisal abilities. In a broader sense, research helps the healthcare professional to keep abreast of continuing scientific advances and decide which of these should be incorporated into routine clinical practice. WUK

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Key points

- When undertaking research, a simple, focused and clear research question (hypothesis) is an essential initial requirement.
- Sample size calculation is a vital part in the planning of a trial since it prevents erroneous results on completion of the study.
- All studies that need access to patients, patient records or patient data require approval from the appropriate ethics committee.
- Consent for research is required by law and failure to obtain consent is a violation of patient's moral right of respect for autonomy.
- Researchers should always strive to maintain the highest standards while conducting and reporting their research findings — that is with utmost honesty, integrity, openness and accountability.

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