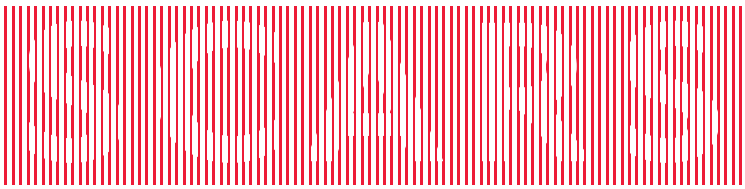
IMAGINE A WORLD WITHOUT



THE FREE FOUNDATION

MAKING A WORLD WITHOUT SCARS A REALITY

PROFESSOR SIR BRUCE KEOGH

If our aspiration to achieve scar free healing within a generation is realised, the impact on a wide range and number of conditions will be enormous. From trauma, military injury, burns, surgery and complex wounds, as well as internal fibrosis and scar related diseases of the major organs – the potential economic and health benefits are staggering.

This strategy sets out to make real our bold and exciting vision of a world without scarring. The United Kingdom remains uniquely placed to drive this programme of work, to take full advantage of some of the world's leading bioscience research teams and a partner with the unique clinical research setting of the NHS.

The time has never been better to embark upon this journey. We owe it to the many millions worldwide affected by the functional and emotional challenges of scarring and disfigurement, to implement this strategy with passion and to deliver scar free healing within a generation.

Professor Sir Bruce Keogh

National Medical Director
NHS England

"There has never been a better time to embark on the pursuit of scar free healing. With the right leadership, collaboration and support new therapies are within reach.

The UK is well placed to lead and The Scar Free Foundation is the right organisation to make this happen.

Scar Free healing in a generation is a challenge but I believe we can get there".

Professor Sir John Gurdon

Joint Winner of the Nobel Prize for Medicine 2012

PROFESSOR MAGGIE DALLMAN

Development of this scar free strategy represents an enormous collaborative effort by a group of leading scientists, engineers and clinicians across and beyond the UK. On behalf of The Scar Free Foundation, I am indebted to the Scar Free Advisory Panel as well as other colleagues in the scientific and medical community for their assistance. I also acknowledge the invaluable contribution of those clinicians and carers throughout the UK who assisted with the framing of the clinical and patient focused questions as well as those patients and clinicians who participated in the surveys.

Scarring, which encompasses the life threatening internal fibrosis associated with many diseases, remains an enormous challenge but with leadership, collaboration and support it can be addressed. We are now perhaps uniquely well placed to harness the power of our combined scientific strengths in pathway biology, stem cell research, comparative biology and human genetics together with those in bioengineering, physical and mathematical sciences to achieve this clinical goal.

I hope to look back on the publication of this work as a watershed in the delivery of new understanding and treatments that can benefit the millions of people affected by scars.

Professor Maggie Dallman

Chair, Scar Free Advisory Group
Associate Provost (Academic Partnerships)
and Professor of Immunology, Imperial College London

SCAR FREE STRATEGY

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EXECUTIVE SUMMARY

In 2015, The Scar Free Foundation Board of Trustees mandated the development of a major programme of research to deliver scar free healing within a generation.

The Scar Free Foundation Research Council appointed an Advisory Group, led by Maggie Dallman, Deputy Chair of the Research Council, Associate Provost (Academic Partnerships) and Professor of Immunology at Imperial College London. The Advisory Group comprised representatives of clinical and patient communities and leading centres of academic excellence in relevant disciplines.

The objectives of the Advisory Group were to:

- Develop a research framework to support the delivery of scar free healing;
- Ensure concurrence in the development of the scientific and clinical research strategies in pursuit of scar free healing.

The Advisory Group's membership is detailed at Appendix 1.

Between October 2015 and April 2016, the Advisory Group worked to develop a framework that would reflect the broad and challenging nature of the problem and that would identify the key areas for research required to deliver scar free healing.

This document details an integrated clinical and basic sciences framework (Figure 1), interdependencies of the imperatives, initiatives and enablers are illustrated in the 'Roadmap to Scar Free Healing' (Figure 3).

Summary of Key Recommendations

- A broad programme of integrated biological, experimental and clinical research should be underpinned by contributions from the physical, engineering and mathematical sciences;
- Improved patient outcomes should lie at the heart of the strategy and drive the research programme;
- The Scar Free Foundation's role should be to nucleate a nationwide effort and leverage resource from other funding agencies, industrial partners and government;
- A strong coordinating and leadership function is necessary to draw together the community and make the whole greater than the sum of the parts.

SETTING THE SCENE: BACKGROUND TO THE SCAR FREE STRATEGY

The Scar Free Foundation (formerly known as the Healing Foundation), was established in 1999 by the British Association of Plastic, Reconstructive and Aesthetic Surgeons, with the aim of funding research into the improvement of treatments for the benefit of people who live with the physical and psychological challenges that result from a physical disfigurement or visible functional impairment.

From its inception, The Scar Free Foundation has placed the patient at the heart of its activity, both through regular input from people with first-hand experience of disfigurements and impairments (Scar Free Foundation Ambassadors), and by focusing on projects with clear potential for clinical impact and translation into routine care.

The Foundation's first research strategy was formulated following a priority-setting exercise overseen by the then Research Council Chairman, Professor Sir Ken Calman. The first priority projects were identified as follows:

- A Centre for Tissue Regenerative Medicine;
- A Centre of Burns Research;
- A Major Project on the Psychology of Disfigurement;
- A Patient Information Project.

Major Successes of the Previous Strategy

The strategy was revisited in 2006 under the Research Council Chairmanship of Professor Sir John Temple and the goal of establishing a centre for cleft lip and palate research was added, along with a defined programme of project, fellowship and elective awards.

The Healing Foundation Centre for Tissue Regeneration at the University of Manchester has delivered 10 years of high quality research, centred on the repair systems of animals that heal without scars, and has also undertaken scientific and clinical research into non-healing diabetic wounds.

The Scar Free Foundation's research programme in cleft lip and palate includes the Cleft Collective Gene Bank at the University of Bristol, which is the world's largest cleft DNA bio-resource. For the past two years, The Scar Free Foundation funded team have been collecting blood samples from children (and their families) born with cleft along with detailed family histories with proposed lifetime follow-up. This endeavour is the most coordinated effort ever undertaken to understand better the causes of cleft and contribute to improved treatments.

The Scar Free Foundation's investment in burns research, the Burns Collective, is a networked programme of clinical research across four universities and three hospitals. The Burns Collective has undertaken extensive research into the clinical management of burns, including the development of smart dressings that detect infection in burn wounds, prevention, and a prospective observational cohort study that aims to study in parallel the inflammatory, immune, endocrine, metabolic and coagulation responses to severe thermal injury in children and adults. The Collective has also undertaken a range of research into providing support for children with burn scars in their psychosocial adjustment.

Since its establishment, the Foundation has been actively involved in the building of research capacity and capability. In addition to a range of student Elective awards and Fellowships, the Foundation manages the British Society for Surgery of the Hand (BSSH) Clinical Associate Professorship in Hand Surgery at Nottingham University. The aim of this latter award is to promote high quality multi-centre clinical research in common hand conditions.

The Appearance Research Collective established by The Scar Free Foundation undertook a major project into the psychology of disfigurement. This work culminated in the publication of CBT for Appearance Anxiety, which is already considered to be a required text in NHS clinics.

The New Strategy

By 2013, the Foundation had achieved all the aims articulated in its first research strategy and over the course of 14 years in operation had made possible over twenty million pounds of important, life changing research in wound healing and disfigurement.

A 'Strategic Review' of activity was undertaken to assess operational priorities within the Foundation's principal fields of interest. Key stakeholders including donors, researchers, patients/families and clinicians were engaged to understand the current 'state of patient need', those areas where already recognised need remained unmet and the potential role of The Scar Free Foundation in meeting those needs.

From this review, the Foundation's priority areas were set. These priorities were identified as follows:

- Cleft and craniofacial conditions;
- Burns and thermal injuries;
- Repair and regeneration, and
- Aesthetic treatments.

As well as a principal theme of research across these priority areas, other 'work streams' to be considered included prevention, information and awareness, psychology and rehabilitation.

The Scar Free Foundation then consulted with its Principal Member organisations (Appendix 2) and invited them to submit their 'big questions' in their respective areas.

From these 'big questions' the overarching theme of scar free healing emerged and the prospect of a major research programme to develop scar free healing within a generation gained increasing traction. It was felt that this bold pursuit built on earlier successes and represented an advance in both ambition and scale of the Foundation's activities.

In January 2015, The Scar Free Foundation Board of Trustees mandated the development of a major programme of research to deliver scar free healing within a generation.

Introducing the Problem

Scars are common, costly and can seriously change lives. Scarring is caused by a variety of accidents including burns and trauma, and by surgery used to repair congenital conditions in children or diseases like cancer. The painful emotional challenges of living with visible scars can last a lifetime. Wounds cost the NHS billions of pounds every year and impact on thousands of lives. In 2014-2015 19,239 people in England and Wales sustained a burn injury which required hospital care. Since 2004 more than 140,000 burn injury cases have been recorded on the International Burn Injury Database. The total cost to the NHS of these treatments and care is huge. Many people face great pain, restricted function and deep psychological anxiety because of hard to heal wounds and scarring conditions.

Scarring and fibrosis are also implicated in broader conditions, such as chronic leg ulcers where patients experience extensive scarring which also delays recovery – and drug reactions resulting in scarring after the healing of the primary condition. Examples include Stephen-Johnson syndrome, Lyell syndrome and the rare skin disease dystrophic Epidermolysis Bullosa. Beyond this, fibrosis underlies the pathology of many chronic diseases that may be of particular prevalence in an aging population. Regardless of the organ or tissue involved, it appears that similar pathological processes are at work, and common mechanisms driving disease exist. Therefore, understanding one fibrotic disease will also lead to significant and widespread advances in a number of common human diseases (such as liver cirrhosis, scarring in diabetes and atherosclerosis). Thus, the implications of scarring are particularly far-reaching and have a considerable impact on people's lives. The potential of scar free healing is enormous.

The Scarring Process

Mammals have a very efficient healing system, which allows the body to repair rapidly following injury. However, the speed of the tissue repair process, essential in preventing fluid loss and infection, does not allow perfect tissue regeneration and often results in the formation of a scar, which can be further exacerbated by, for instance, concurrent infections.

Scarring itself is the production of excessive amounts of connective tissue in the course of reactive and reparative processes. Scar tissue can develop in individuals with genetic predispositions, or can be associated with tissue injury, or as a pathological consequence of an underlying fibroproliferative disease such as Scleroderma. Excessive scarring presents a major unsolved therapeutic problem, as there is a

paucity of effective treatments. However, there is currently considerable therapeutic opportunity for the development of anti-scarring therapies, as the last decade has seen significant advances in our understanding of the scarring process. These advances have not been realised, due in part to the biological complexity of scarring, and in part to the challenges presented by the use of anti-scarring agents. These challenges include:

- Which agents should be used and in what setting;
- At what stage of the scarring process; and
- For how long?

Scarring usually follows a primary insult or injury that leads to tissue and organ damage. Injury that characteristically involves inflammation leads to the initiation of the normal healing response. The inflammatory phase initiates the repair process within the damaged tissue and results in the resolution of damage in an attempt to return the tissue to its normal function. Although scarring is part of normal tissue repair, abnormal molecular and cellular mechanisms (present in various scenarios including infection, background susceptibility, chronic, persistent or severe injury or autoimmunity) can drive and exacerbate the repair process and result in excessive scarring or fibrosis and loss of tissue and ultimately organ function.

Understanding the cellular and molecular mechanisms of scarring and fibrosis is a high scientific priority, as almost 50% of all natural deaths in the western world can be attributable to chronic fibro-proliferative and scarring disease.

The key outstanding questions

The different phases of injury, repair and resolution involve the carefully orchestrated interplay and crosstalk between many cell types (inflammatory, immune, resident and circulating cells), all of which are programmed to function within genetic, molecular and environmental constraints. Each of these cell types will perceive many stimuli and respond accordingly to activate specific genes and produce proteins that activate complex pathways, which in turn will result in the required outcome of successful damage repair. However, with the level of complexity of these processes, pathway aberrations can result in very abnormal outcomes such as chronic inflammation, impaired resolution, persistent scarring and cellular response to the altered tissue microenvironment. Furthermore, genetic heterogeneity adds to the complexity, resulting in patient cohorts that respond differently to treatments and therapies. This complexity is exacerbated considerably by microbial factors that may contribute to the development and progression of scarring, but this adds a huge variable to the project and thus will be explored to the extent possible within the scope of the research programme.

The Scientific Framework

This framework aims to address the problems and the questions outlined above by putting the patient at the centre of a holistic strategy covering both clinical and basic science research.

Section 1, the clinical research strategy, addresses prevention, standardisation of care, and the culture of research and clinical trials, identifying some key potential impacts and outcomes.

Section 2, the basic science research strategy, comprises five core imperatives. Pathway Biology, Stem Cells and Regenerative Medicine, Comparative Biology, and Human Genetics are the basic areas that will be underpinned by Bioengineering and the Physical and Mathematical Sciences.

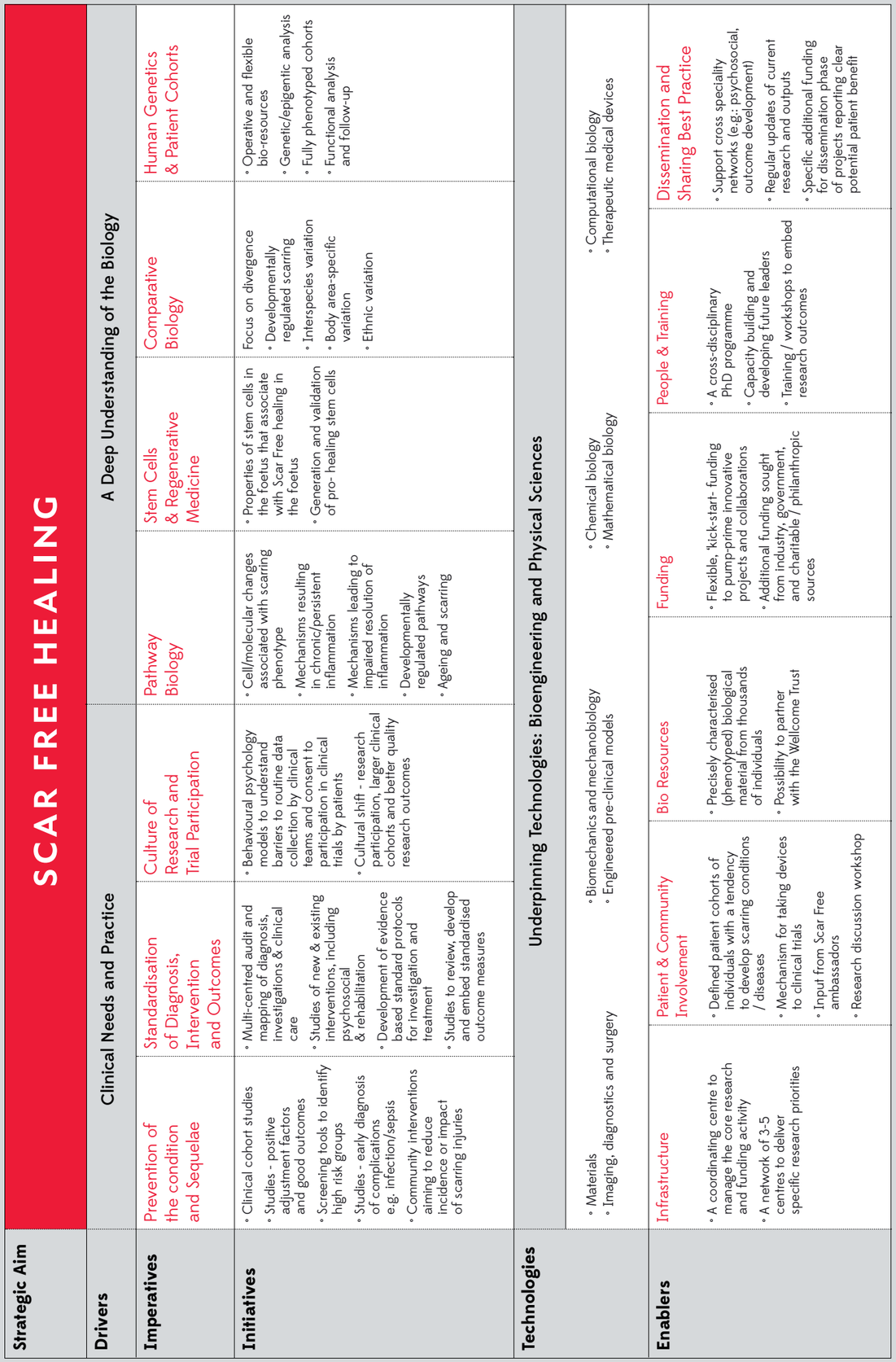
The delivery of the strategy will only be made be possible with effective experimental medicine projects, including early stage clinical trials. This is addressed in Section 3.

A number of enablers have been identified as important facilitators for the effective delivery and coordination of integrated clinical and basic science research strategies, and these factors are detailed in Section 4. It is anticipated that responsibility for fully defining these enablers will lie with the Delivery Group (Appendix 3).

Finally, the Scar Free Advisory Group has identified the key impacts, outputs and outcomes that scar free healing will deliver. These are detailed in Section 6.

The Scar Free Advisory Group was appointed to reflect the broad nature of the clinical and scientific challenges presented by such a complex and multifaceted phenomenon as scarring. The areas to be explored as part of the programme of research were identified by the Advisory Group as being the key imperatives that, as part of an integrated and complementary research strategy, will enable scar free healing within a generation. Each of these imperatives has the potential to deliver improvements in the treatment and management of scarring or to alter the physiological or immunological response that would typically lead to the development of a scar. However, the most significant value of the scar free healing programme of research lies in the coherent and integrated nature of the strategy, bringing together the various differing but complementary disciplines to deliver solutions to cross-disciplinary problems.

Figure 1



VICKY HORSMAN

I still see the scars when I look in the mirror. But I also see myself as a stronger person. I've changed my outlook on life. I don't take anything for granted anymore. I wouldn't be where I am now without the work of doctors and surgeons, it's amazing what they can do. Having the right support from people around you really does make a massive difference. To anyone going through a similar experience to mine, I'd say never give up. Look forward and put what's happened in the past behind you. You can definitely still get everything you want out of life.

SECTION 1: CLINICAL RESEARCH STRATEGY

Background

The Scar Free Foundation has the experience of and an established reputation for, creating successful partnerships between academic and clinical colleagues, as well as with pharmaceutical and medical appliance companies. This model of working will provide a strong basis for the successful delivery of the scar free strategy. The NHS, as the national provider of healthcare, has the potential to provide a unique platform for this networked and co-ordinated programme of research, enabling the creation of bio-resources and large patient cohorts to both inform and trial major developments in the journey towards scar fee healing.

To engage fully with the clinical community, the Scar Free Advisory Group used consensus agreements from each of The Scar Free Foundation Principal Member organisations as the basis for follow up interviews with leading clinicians and researchers. In the period May – November 2015, twenty senior clinicians/academics from twelve different research centres were interviewed. Where possible, more junior researchers and research nurses provided insight into day-to-day challenges. Questions were structured using The Scar Free Foundation's priority areas, with the aim of identifying current gaps, immediate priorities and information about the best ways in which The Scar Free Foundation could facilitate research in practice.

Summary of findings

There is universal agreement on:

- The need to place the patient at the centre of the scar free strategy by continuously asking the question, 'what will be the impact for patients?' and by including patient representatives throughout the process of shaping and allocating funding. Clinicians prioritise studies leading to measurable change in the clinical setting, with a demonstrable impact on routine practice.
- The need to standardise care. This ranges from need for agreement about diagnosis, definitions and interventions, to protocols for standardised care pathways including psychosocial input and rehabilitation, and the development and routine use of standardised clinical and patient reported outcomes.
- The specialist nature of reconstructive plastic surgery and associated specialities often involving specialised care for patients, i.e. small numbers of patients who receive high cost care provided at a small number of services. This means that numbers are relatively small (compared with larger surgical specialities). Therefore, a collective approach to research involving research trial networks and close collaboration and coordination between centres is likely to produce better quality outcomes.

There is a very strong consensus that an emphasis on basic sciences should not be at the expense of the clinical agenda, and especially the needs of those who already live with scarring.

Therefore, rather than divide the scar free strategy into separate basic science and clinical strategies with different funding streams, a single research strategy has been developed to incorporate both and maintain the guiding principle that the patient sits at the heart of the research agenda.

Imperative 1: Prevention of the Condition and Long-Term Sequelae

The Scar Free Foundation has invested in better understanding cleft by funding the DNA gene bank at Bristol University. This resource has made possible the investigation of both genetic and environmental factors that cause cleft and lead to the development of the condition over both the short and long-term. This is a key resource for scar free healing research, as it provides the best way of understanding the impact of the numerous and complex variables that affect the cause, course and management of pathology, and it should continue to be funded in the long-term. This also provides the model for development of similar resources across the different specialities, and the possibility of expansion to include further conditions is addressed under Imperative 7 and should be considered during the delivery phase.

Prevention is particularly important in burns and trauma. As one Scar Free Foundation Centre Director commented, "the best way of avoiding scarring is to prevent injury from occurring." Similarly, understanding the predictors and management of complications associated with wound healing, infection, and sepsis is an important priority in respect of preventing the severity of scarring.

Within the field of reconstructive surgery and trauma, there is a very large number of patients who experience life changing functional loss from severe infection (such as meningitis and group A streptococcus) to limb trauma. This impacts upon cosmesis, self-worth and psychological well-being. In order to improve the current provision of care, it is important to understand the factors that lead to the best outcomes for this group and to support long-term physical and psychological rehabilitation. There is the scope for this field to become a new specialism managed by clinicians with the integrated pursuit of reconstruction, rehabilitation, and psychosocial integration.

There is a growing minority of people for whom aesthetic surgery and non-surgical interventions result in poor outcomes. There is the potential for effective psychological screening to reduce harm for those at risk, promote alternatives and avoid scarring. The Scar Free Foundation has funded research to develop an effective and easy to use screening tool, but funding is necessary for dissemination. Similarly, good information for patients is required, but this is contingent on improved knowledge of the long-term outcomes for people undergoing aesthetic procedures.

The Scar Free Foundation funded a large-scale psychological project examining the factors and processes associated with positive adjustment in adults with a visible difference. These findings were used to design and develop interventions for adults. There remains a need for a similar study with children and young people who are managing existing scarring and differences in appearance and function resulting from congenital anomalies.

Imperative 2: Audit and Standardisation of Clinical Care

Measuring Outcomes

The routine collection of outcomes is key to effective audit, understanding the effectiveness of current and new interventions, identification of best practice, and improvement of services throughout the NHS. Other surgical specialities, such as orthopaedics, have made progress in this area. The Scar Free Foundation has already funded research in this field, including as part of the Cleft Collective and the Burns Collective, but further research is still necessary to develop instruments to measure outcomes reliably in areas such as speech, appearance, dental appearance, dental development, hearing, general paediatric development, and long-term outcomes.

There has been some progress within the field of plastic surgery, with notable examples including the national audit of breast reconstruction that agreed key outcome measures (including BREAST-Q), and the Hand Registry that was set up as part of the international composite tissue transplant programme. Systematic data collection has also been achieved by those working with military personnel, but the data is yet to be thoroughly analysed. However, this work is not representative of plastic surgery and trauma as a whole, where the development and routine use of outcome measures remains a priority.

The most fundamental priority in the context of the mission to achieve scar free healing, is the development of instruments to reliably measure scarring and its physical and psychological impact.

Diagnosis and investigations

Early diagnosis and investigation remains a challenge. For example, early diagnosis of 'clinically relevant' infection in burns is necessary for targeted management and to promote wound healing. Similarly, the differentiation of infection (colonisation and true wound infection) and sepsis is extremely difficult.

The type and timing of investigations varies considerably between units.

Similarly, to facilitate the development of individual patient-centred care, the identification of early predictors of outcome (both intrinsic to the patient and extrinsic) following treatment is necessary.

Within the aesthetic field, diagnosis of patients with psychological conditions such as Body Dysmorphic Disorder remains difficult, with no standardised approach and no robust evidence about whether or not this group are contraindicated for surgery.

Accurate audit of 'usual care' will involve agreement about definitions and diagnostic criteria as well as robust processes for data gathering including quality control and designated responsibility for patient recruitment.

Interventions

There are no standards for best practice across all specialities, and there is no standardisation of care even for common conditions (such as nail bed injuries). Thus, a child admitted to a burns unit in one part of the UK will not necessarily receive the same care as a child admitted elsewhere. For example, the use of biological dressings in small burns varies significantly across burns services. Furthermore, outcomes related to skin grafts in small burns vary 7-fold across the UK. Thus, both process and outcomes vary.

Burns research: investigation into how to achieve consistent wound management and critical care in the first 48 hours was highlighted as a significant priority. This includes agreement about the extent of debridement, use of antibiotics and type of dressing.

The Scar Free Foundation is currently funding research at The Scar Free Foundation Centre for Burns Research, Birmingham into the effectiveness of pressure garments. This is a good example of an intervention that is widely used as part of long-term management without any evidence for its effectiveness in reducing the severity of scarring.

Plastics and trauma: there is no agreement about intervention and best practice throughout the patient journey, including longer-term rehabilitation. Even well-established surgical procedures involve a level of variability in practice because patients are unique in terms of their precise anatomy, injury and underlying condition. Individual surgeons may develop their own variation of an established technique. Agreement is needed to describe the key variables in surgical, psychological and other therapeutic interventions before comparative studies can be completed. Standardisation is required in respect of all relevant conditions, but it will be necessary to prioritise in light of limited resources – and it is thus recommended that burns, cleft, trauma and plastics are prioritised ahead of others, since these areas offer the most immediate opportunities for evaluation of the scar free technologies being developed through the basic science strategy.

Psychosocial care: provision is variable and in general there is a lack of awareness of completed research, such as the predictors of positive psychological adjustment. The effectiveness of new and existing psychological interventions requires investigation for both adults and children. The Scar Free Foundation will not lose sight of those people who have existing scarring, including military personnel, and research will continue into the support and management of these groups over the long term.

Aesthetic surgery: the benefits or long-term safety of procedures, including liposuction and body contouring, have not yet been assessed. Effective audit is needed to establish the benefits, if any, and to help prevent the growth of new, unproven and possibly unsafe or harmful surgical and non-surgical treatments (such as fillers), and to provide accurate patient information.

Across all specialities, there is a lack of agreement regarding care protocols and pathways of care. Developing these standards will depend on a commitment to audit and routine data collection, together with the appropriate resources to support and embed a culture of evidence-based practice.

Imperative 3: Promoting a Culture of Research and Trial Participation within Clinical Teams and Patients

Within the field of behavioural psychology, comprehensive models of behaviour change have the potential to facilitate understanding of the barriers to routine data collection by clinical teams and consent to participation in clinical trials by patients. The aim of this research is to achieve a cultural shift towards greater research participation, development of larger clinical cohorts with associated methodological opportunities and therefore better quality research outcomes.

HEMANI MODASIA

I don't feel like I'm different from anyone else, but at the same time,
I know that I am. There are the differences you can see, the physical impact
of scars, but it's the emotional component that stays with you forever.
A world without scars is something I could never have even contemplated,
and for me, it talks as much about the emotional impact as anything else.
In my work as a doctor, perhaps because of my experiences, I try not to see patients,
but people. That's why for me scar free healing is an amazing medical ambition,
but what's really exciting is what it's going to mean for people's lives.

SECTION 2:
BASIC SCIENCE RESEARCH STRATEGY

Imperative 4: Pathway Biology

An overarching objective of this imperative is to apply pathway biology, systems biology and related approaches (including genomics, transcriptomics, proteomics and metabolomics) to obtain an integrated view of the cell and molecular changes associated with the scarring phenotype. This approach will enable the assembly of an enhanced and definitive understanding of the basic mechanisms that underlie scarring pathways and networks to provide therapeutic advantage and lead to the development of effective anti-scarring treatments.

Major themes that impact upon scarring are:

i) Chronic and Persistent Inflammation

Although in almost all forms of scarring inflammation is an early and critical insult (initiated by tissue damage [surgical/burns], infection, autoimmunity and foreign material), and the contribution of inflammation as a trigger is clear and takes place in the earliest stages, there is mounting evidence that both persistent and chronic exposure to inflammatory stimuli results in excessive scarring.

ii) Impaired Resolution

The resolution of inflammation and thereby the repair process can be affected by immune processes (autoimmunity) and failure of the correct resolution. The tempo and pitch of inflammation are also believed to be major determinants of the outcome of healing and repair.

iii) Persistence of Scarring

In addition to the factors that drive excessive scarring, such as chronic inflammation, the pathogenic processes associated with persistent or progressive scarring (once inflammation has abated or is controlled) are likely to result from altered or imprinted fibroblast responses. Examples of such pathogenic processes include the biomechanical cues received from the abnormal microenvironment within the remodelling or damaged tissues, and in particular, the production and deposition of abnormal extracellular matrix components in scar tissue. The cells resident in the scar tissue are likely to switch their functional activities in response to these altered environmental stimuli, thereby exacerbating the pathology and thus promoting scarring.

iv) Innervation

Peripheral nerves are known to play an important role in adult mammalian wound healing. Following wounding the tissue can develop a dense nerve networks around scars. Here axons form close associations with cells within the wound environment, including endothelial cells, macrophages and myofibroblasts. Sensory nerves are thought to mediate their action on wound repair by the release of neuropeptides, which function as mediators of neurogenic inflammation, regulating blood flow and modulating local immune responses.

Numerous studies in wound models have shown that denervation by either neurotomy or capsaicin causes severe defects in all phases of the wound-healing process, resulting in: delayed wound contraction and re-epithelialisation; reduced microvascular response and neovascularisation; hypertrophic scarring and keloids; decreased wound tensile strength and a delayed and prolonged inflammatory phase.

Possible areas for funding and/or approaches to address the questions:

- **Signal transduction pathways and networks:** Focused studies centred on exploring the critical roles of known pathways in scarring, for example TGF beta/Smad/TAK1 and other core developmental pathways that appear to be re-activated or recapitulated in scarring (such as Wnt/Notch/Hedgehog/Hippo).
- **Hypoxia inducible factor (HIF) and the HIF hydroxylases:** This area is a potential target for improving wound healing, and small molecule inhibitors of HIF hydroxylases are currently being trialled in man by several companies following promising results in a variety of animal models. However, this area has a poor record for translation from animal models, for reasons that are not clear. HIF hydroxylases are one example of many potential targets for this type of process. The major challenge is target selection but this could be addressed.
- **Inflammation:** Exploit our knowledge of inflammation to selectively and potentially alter the course of scarring by targeting inflammation and modulating critical cell phenotypes (such as macrophage polarisation).
- **Resolution pharmacology:** Harness resolution pharmacology in pathway biology to define the inflammatory-scarring axis and to enhance repair and reduce inflammatory-driven scarring processes in translational models and promote scar free repair.
- **Cellular energy metabolism:** Investigate modulation of energy metabolism to promote switching between glycolysis and oxidative phosphorylation to control scarring.
- Cell ablation therapy: Explore the potential to refine cell ablation therapies by focusing on the role of immune cells (B and T cell subsets), and progenitor populations in scarring (fibrocytes, pericytes and both EMT and EndoMT).
- **Epigenetics in scarring:** More detailed definition of the role of epigenetics in tissue scarring.
- **Ageing and the scarring process:** Explore age-related changes in the scarring process and the non-healing wound scenarios.

Critical elements required to address the key questions:

- **Patient Cohorts:** Develop and utilise defined patient cohorts of individuals with a tendency to develop scarring conditions/diseases (including congenital, injury/trauma, hypertrophic scarring, infection, and inflammation) to investigate (using biological samples) intrinsic pro-scarring pathways and biomarkers and potential anti-scarring agents.
- **Proof of mechanism:** Support studies to define pathways and evaluate existing and new drugs in pre-clinical and novel models (3-D/novel models) of scarring and repair.

Imperative 5: Stem Cells and Regenerative Medicine

The capacity of humans (and mammalian model organisms) for scar free healing during their early foetal stages provides a compelling mandate to seek a fundamental understanding of the mechanisms underpinning scar free healing in order to acquire the future capacity to confer this ability postnatally. Our current understanding of foetal capacity for scar free healing remains incomplete; however, there is evidence for contributions of unique foetal immune and inflammatory responses, of unique foetal wound cytokine milieu, and unique foetal tissue stem cell compositions. Therefore, research is needed to delineate the contributions of these mechanisms, and others, to foetal healing capacity. While the scarring process that occurs following post-natal wounding is clearly multi-factorial, insight into the stem cell origins, proliferation and differentiation of the fibroblasts and other cells responsible for healing and scarring is of particular importance. Finally, research is necessary to identify the cellular mechanisms of healing and scarring where interventions may be possible using stem cell-based therapies.

This imperative includes the need to understand not only how stem cells are involved in the healing process, but also how cellular interventions can shift the healing process from scarring to non-scarring. The past decade of stem cell research has enabled paradigm-shifting insights and research tools at the interface of developmental, cellular and molecular biology and human genetics. These insights and tools include a massive acceleration in our knowledge of how to guide unspecialised stem cells into potentially useful tissues and organ rudiments ("directed differentiation"), as well as in our knowledge of how one cell type can be converted directly into another cell type through molecular interventions (reprogramming). These advances create an unparalleled opportunity for a quantum leap in our knowledge of healing and scarring mechanisms and their application to scar free healing. The Stem Cell and Regenerative Medicine Imperative shares its objectives with the Pathway Biology, Comparative Biology and Human Genetics imperatives, but emphasises particularly the cellular basis of scar free healing and scarring.

Nobel Prize-winning scientists discovered that mature adult fibroblasts (readily obtainable from scars and wounds) can be reprogrammed as stem cells (turning them into "induced pluripotent stem cells"). Moreover, a conceptually similar approach can seemingly be used to direct the specialisation of the induced pluripotent stem cells into any other cell type (forward programming). These discoveries have created a critical opportunity for scar free healing research. By re-differentiating these induced pluripotent stem cells to adult cell lineages, research resources and potentially cell-based therapeutic resources can be created.

Recent advances in regenerative medicine have also led to the use of mesenchymal stem cells (MSC) as regenerative therapies in wide ranging fields of medicine. Significantly, these cells can be harvested with ease and in abundance from patients' fat. This opens up the possibility of using the patient's own cells in personalised treatments. Currently, there are clinical trials exploring the use of MSC in areas such as chronic wounds, burns, scarring, fat grafting and aesthetic surgeries. None of the several hundreds of patients recruited to these trials have experienced a serious adverse event, which demonstrates the safety of this approach.

Key research objectives in this Imperative:

i) To understand mechanisms of scar free and scar-prone healing in a developmental context

Research is needed to understand mechanisms of scar free healing in a developmental context (foetal healing versus post-natal, juvenile and adult healing). A primary objective should be to identify and characterise in depth the stem cells involved in foetal wound healing (single cell transcriptional profiling of resident cells in foetal wounds). In addition, functional genomic studies utilising mouse embryonic stem cells with knockouts of relevant candidate genes (from the International Knockout Mouse Consortium) are required to understand the molecular genetic basis of scar free foetal healing. Further research utilising transgenic mice is necessary to identify the origin of cells populating the foetal wound.

ii) To acquire capacity to generate and apply stem cells relevant to scar free healing mechanisms

Research is needed to enable cell-based therapy approaches to scar free healing. It will be important to develop methods for directed differentiation and reprogramming of pluripotent stem cells to tissue stem cells and differentiated cells relevant for healing. Stem cells should be modified to express inflammation-inhibiting, scar-diminishing recombinant proteins in the wound-healing tissue context. Research is required to develop cells designed to express and/or educate neighbouring fibroblasts to deploy properly organised extracellular matrices.

These research objectives will enable both in vitro modelling of wound healing using human cells and ultimately, the direct use of the human cells in therapeutic applications. Moreover, an immediate use of the human in vitro cellular models for drug discovery and toxicity testing should be possible.

Possible areas for funding and/or approaches to address the questions:

Funding areas related to objective (i):

- Research comparing cellular origins, composition and phenotypes before, during and after the transition from scar free foetal healing to adult-type scarring.
- Functional genomic studies utilising mouse embryonic stem cells with knockouts of relevant candidate genes (from the International Knockout Mouse Consortium) to understand the molecular genetic basis of adult scarring and scar free foetal healing (relates to Imperatives 2 and 7),
- "Rainbow" (multicolour) mouse studies to identify the origin of cells populating the wound.
- Recombinant inbred mouse studies to identify the genetic basis of scarring (relates to Imperative 7).
- Development of human in vitro stem cell models to study the molecular and genetic mechanisms of scarring (approaches capable of stem cell self-renewal, proliferation and differentiation).

Funding areas related to objective (ii):

- Funding for generation of foetal-type stem cells for transplantation.
- Funding to develop platelets designed to release cytokines and/or their inhibitors.

Funding to develop cells designed to express and/or educate neighbouring fibroblasts to deploy properly organised extracellular matrices.

Imperative 6: Comparative Biology

Tissue repair is a fundamental, evolutionarily conserved process shared by all organisms, but whether tissues repair perfectly or with a scar varies both across species and within a species, including man. By comparing systems, species and situations where scarring does or does not occur, great insights can be gained at the genetic and epigenetic level, but also at the pathway biology level. These insights will inform our understanding of the scarring process and suggest novel targets for intervention.

Focus areas for comparative approach:

i) Developmentally regulated scarring

As alluded to in Imperative 5, perhaps the best-known variation in degree of scarring is that between embryonic/foetal and adult healing – where the former is scar free and the latter leads to scarring. This difference was first reported in mouse and man in the 1990s, and in mouse it appears that the transition from scar free to healing with a scar occurs around two thirds of the way through gestation. Several associated transitions also occur at this developmental stage. The two transitions believed to be most likely causal (and they are almost certainly interlinked) are inflammation (which first happens after wounding, from E14/15) and a change in growth factor profile, with considerable focus on increasing levels of TGFs 1 and 2.

The reproduction in appropriate human models of observations made in other species or predicted from data in silico is crucial to the development of effective therapeutic approaches. These confirmatory models include (but are not limited to) human cell culture, including 3D culture models and the selection of tractable short-term experiments in vivo with clear endpoints and short-term readouts where these are available. A good example of this is the development of Relaxin as a therapy for solid organ fibrosis where, although administration would be required for weeks or months, proof of concept of efficacy in humans and rodents is provided by measuring the immediate effect on myofibroblast contractility in vivo in real time. This then acts as the platform upon which future studies and investment in the longer term can be made.

ii) Interspecies variation

Comparisons between closely related species provide further potential leads. Normal mice scar, but two mouse strains/species have been reported to experience scarring to a far lesser degree. One of these, the MRL mouse, has a complex genetic background – it was initially generated to investigate links between adaptive immunity and lupus, and it famously can repair/regenerate an ear punch wound, but there is controversy regarding the extent to which it scars. More recently, the African spiny mouse was reported to heal very large wounds with almost no scarring; this remarkable healing might have evolved alongside a strategy for ripping itself free of predators, much like lizard tail release. These two strains of mice have not yet revealed clues as to genes/signalling pathways associated with scarring but both display an altered inflammatory response.

Comparing mutant mice, which cannot raise an inflammatory response, with control mice that are capable of raising such a response confirms that inflammation is a likely player because these mice do not scar, and further microarray comparison of these mice reveals genes that are downstream of inflammation and might drive scarring. One of these, osteopontin, can be knocked down in a mouse skin wound and this considerably reduces scarring. Similarly, knockdown of TGFs 1 and 2 at the wound site will also reduce scarring. Therefore, it would appear that modulation of the inflammatory response and/or associated growth factor signalling pathways might be good therapeutic strategies.

Several well-studied model species that also demonstrate the capacity to regenerate appendages and organs can reportedly also heal adult tissues in a scar free fashion; prime examples are axolotls and teleost fish. The latter actually first heal with a transitory deposition of collagen and then resolve this "scar". This has led to the speculation that adult mammalian tissues, and not fish, may induce enzymes at the repair site that direct persistent pro-fibrotic collagen cross-links.

iii) Body area specific variation

Some parts of the body heal with variable eventual scarring. It is well known that oral tissues of the mouth heal rapidly with very little sign of scarring; they also exhibit an altered growth factor profile and dampened inflammatory response. The liver is the organ with perhaps the best regenerative capacity of any tissue in the body and it has some capability to resolve scarring, which is, in part, mediated by macrophages. A linear scar from neck to groin will scar more over the chest than at either end and this is probably because increasing tension leads to mechanical activation of a more robust inflammatory response. The UK has research strength in the field of solid organ fibrosis and a component of this strategy will be to interface with this community and to evaluate and rapidly deploy promising approaches identified and developed in this parallel work.

iv) Ethnic variation

There is a clear genetic link across humans associated with scarring, with some races experiencing scarring to a greater degree than others; for example, keloid scarring is very much linked to dark skin, and so human genetic approaches have been/are being considered as a route to uncovering scarring genes that will be the targets for anti-scar therapeutics. Research funded by The Scar Free Foundation, undertaken by Husam Bella on patients in the Sudan indicated that keloid disease is associated with susceptibility genes.

Possible areas for funding and/or approaches to address the questions:

- Identify optimal comparator models for analysis via discussion with the relevant community.
- GWAS/RNA Sequencing/proteomic analysis of comparator materials. Identification of novel genetic/epigenetic components that associate with enhanced healing or scarring, or scar resolution.
- Live imaging approaches with fluorescent reporters of cell (e.g. inflammatory cells and fibroblasts) and molecular (e.g. collagen) players (in translucent zebrafish or intravital microscopy in mice) to capture and observe the scarring process in real time.
- Recapitulation of reduced or enhanced scarring through genetic manipulation to ensure authenticity of identified components.
- Feed through into pathway biology for identification of putative regulatory mechanisms.

Imperative 7: Human Genetics

Changes in our knowledge of the human genome and the rapid development of technologies to measure complete catalogues of variation of the genome in individuals will contribute fundamentally to our understanding of scarring. The first complete record of the Human genome, published in 2001-02, took 15 years to complete and was undertaken at vast expense. Since then, the ability to measure the complete genome of an individual in less than 72 hours and at a cost of less than $1000 has been realised. The combination of this capacity with well-curated and large population based/clinical collections has ushered in a new era for the study of complex health and disease outcomes, of which scarring is a prime example.

Genome-wide association studies (GWAS) have been pivotal in the identification of genomic regions associated with complex diseases or traits. Findings from these studies have already had an impact on aetiological understanding and clinical practice by improving risk prediction, disease classification and drug development. GWAS findings have been used to reclassify individuals as high-risk for cardiovascular disease based on genetic profiles, and to develop more refined molecular taxonomies for different types of cancer. The opportunity now exists to draw upon this experience and complement or supplement these established methods with whole-genome sequencing to understand the genetic basis of scarring.

Focus areas include:

i) Operative and flexible bio-resources

Success in deploying bio-resources will depend on being able to access large and well-curated data collections of patients and representative participants. Above all, effective genetic analysis of the propensity to scar and of the biological pathways and risk factors pertinent to scarring will hinge on the availability of precisely characterised (phenotyped) biological material from thousands of individuals (the bio-resource). The presence of common and small genetic effects or larger, but rare, effects will necessitate the enhancement of analytical power through a combination of (i) precise biologically relevant measurement (from the molecule to case status) and (ii) substantial sample sizes (numbering in the thousands).

Patient phenotyping is crucial to the successful deployment of these modern genetic and epigenetic analyses. The nature of the lesions that comprise the bio-resources mean that measurements of the extent of initial injury (such as cleft lip, cleft lip and palate, among others) are readily available and recorded. Similarly, the dates and detail of any intervention or treatment and the time frame in which healing and scarring occur are also recorded.

Despite recognition that the susceptibility to scarring is heritable, the genetics of scarring have not been investigated systematically. The Scar Free Foundation has sought to address this by funding the aforementioned bio-resources, including the Cleft Collective Gene Bank, which provide opportunities for genomic and epigenomic studies of scarring. The physical scars in these children can also be recorded (using 2D and 3D imaging), and potentially so can the emotions related to scarring (the clinical characterisation or phenotyping). Furthermore, conditions with different aetiologies, such as keloid (which has also received research funding from The Scar Free Foundation) or populations with a high prevalence of caesarean section (and therefore scarring) can be accessed.

The availability of DNA from children born with cleft (via the Cleft Collective Gene Bank) and the potential to acquire material from patients with burns provides an opportunity to investigate the genetics of scarring, irrespective of the cause of the lesion at a genome-wide level. Identifying genomic regions important for scarring processes can potentially indicate modifiable pathways to scarring and improve the management of scarring. Moreover, it can contribute to identifying those at high risk of scarring following surgical procedures. For the last two years, fibroblasts from patients have been stored in bio-resources to provide a resource for generating induced pluripotent stem cells (see Imperative 5).

Populations with a high prevalence of certain routine surgical procedures (such as the 65% prevalence of caesarean sections in Brazil) provide a further opportunity to understand the genetic basis of scarring through the use of routinely collected phenotypic data. The availability of detailed physical examinations or relevant clinical data alongside genetic data will be necessary to help provide the opportunity to systematically assess the genetic contribution to variable scarring responses. Another example of this type of resource is the use of natural, population-based, challenge experiments that can, with the correct support and researcher capacity, yield completely novel information as to the biological contribution to scarring.

ii) Genetic data collection capacity

The access to appropriate collections of participants, material, DNA samples and physical data will of course be of maximum value when combined with genetic and omic data. Expertise for the coordination, management and undertaking of new genetic and omic data collection is required to meet the demands of concentrated efforts to examine the genetics of, and related to, scarring.

iii) Functional analysis and follow-up

The discovery of genetic variants that increase the risk of, or protect against, scarring can, once identified, open up the possibility of functional studies. These can be undertaken in cellular models, for example from cell lines developed from tissue. Such work can be complemented where relevant with studies using invertebrate and lower vertebrate models to dissect out the relevant mediators mechanistically and regulating them to model potential therapies.

Overall, this genetic approach has the potential to identify not only therapeutic targets directly, but may also highlight pathways, cellular messengers and signals that have not previously been suspected as having a direct bearing on scarring. Moreover, the approach will ultimately identify predisposing variants irrespective of the cell type in which the variant is active in mediating the scarring process.

Possible areas for funding and/or approaches to address the questions:

- The application of genetic approaches to define predisposition to, or protection from, scarring is now extremely timely.
- Biobanks and bioresources such as the Cleft Collective Gene Bank, places the UK research community in a perfect position to exploit the rapidly developing technology in the field of genetics and genomics for the benefit of our patients as well as expand such bioresources into new patient groupings.

INDIA GALE

A scar is something that happened in the past, yet you still have to take it with you forever. It's a constant reminder of something you don't want to be reminded of. I don't think it needs to be. If a scar could be something in the past, and nothing else, that would make a huge difference. If there's anything I can do to help someone who's going through what I went through, I'll do it. But more than that, I like the idea that someone else might not have to go through it at all. I think that's an amazing ambition.

SECTION 3: UNDERPINNING TECHNOLOGIES: BIOENGINEERING AND THE PHYSICAL SCIENCES

Bioengineering and the physical sciences provide underpinning science and technology for modern biological questions. These apply physical and mathematical sciences to analyse, design and manufacture tools, structures and processes to advance the life sciences and for the benefit of human health. The key is that, for the first time, this community of scientists and engineers will be engaged in a targeted and coordinated fashion in order to capture their expertise to solve the problem of scarring.

Many different approaches are taken in this domain that can be applied to move forward the research and translation imperative for scar free healing. This non-exhaustive section groups the proposed research into eight key areas.

Focus areas include:

i) Materials engineering in regenerative medicine, including wound healing

The opportunity in this area is to monitor cells and tissue formation using engineering technologies and physical sciences, including mapping the chemistry of cells and tissues. The new engineering technologies can be harnessed for tissue repair. The overall aim of this area would be to gain a balance in the complexity of biomaterials design for translation. Current techniques allow advanced and complex biomaterials to be developed, yet the pathway to translation for these is very long.

ii) Imaging, diagnostics and surgery

The opportunity is to minimise interventions and create new early interventions. Interventions can be optimised based on individual anatomy, physiology and pathology. Examples of such interventions are now commonplace in trauma and orthopaedic surgery, where custom implants, custom surgical guides, and robotic and computer-assisted surgery creates bespoke, minimally invasive interventions. Their transference to scar free healing is timely and would be opportune. Novel diagnostics can be used to follow the post-injury recovery process in real-time to allow timely individualised therapeutic intervention. The aim would be to develop appropriate imaging, image analysis, sensors and surgical tools to provide early diagnosis of scarring markers and allow early intervention to facilitate faster, more effective recovery.

iii) Biomechanics and mechanobiology

The opportunity is to tune the local biomechanical/mechanobiological environment through mechanical treatments (such as active dressings or 'rehabilitation') to accelerate scar free repair; to tune the biomechanical environment to be optimally receptive to regenerative medicine/tissue engineering constructs; and to tune the local biomechanical environment in silico, in vitro and in vivo. The aim of this area is to harness knowledge of force and deformations at the organ, tissue (biomechanics) and cellular (mechanobiology) levels to drive tissue regeneration, reconstruction and repair.

iv) Engineered preclinical models: in vivo and in silico

One opportunity in this area is to use a combination of directed cell culture and microfluidics to develop viable in vitro 'skin-on-chip' models. This overall aim is to develop appropriate animal, in vitro and computational models to allow the study of the biomechanics and mechanobiology of scar free healing and therapy, including biomaterials and regenerative medicine.

v) Chemical biology

The opportunity is to use chemical techniques, tools, and analyses to study and manipulate biological systems, and this often involves compounds produced through synthetic chemistry. The aim is to use chemical principles to modulate systems to investigate the underlying biology and create new function.

vi) Mathematical biology

The use of mathematical models and state-of-the-art statistical methods to analyse biological systems, ranging from stem cells to bacterial organisms, allows the rich dynamical behaviour of these systems, such as the differentiation of stem cells and the development of tissues to be explored. The analysis of such data and the development of quantitative, predictive and explanatory models can help in understanding cellular behaviour, which is key to understanding scarring and the possibilities of scar free healing.

vii) Computational biology

Computational biology is an underpinning technology for scar free healing in which inductive logic programming, as an example, facilitates a data-driven approach to analysing large-volume-data, such as is obtained from screening tests and combinatorial chemistry research. These techniques have been applied both to small molecules (such as ligands) and to proteins.

viii) Therapeutic medical devices

Devices are a key output in bioengineering. Devices such as lasers, ultrasound and mechanical loading on the skin through patches have all shown some promise to facilitate scar free healing. The outputs of many of the areas listed above will result in the design of such medical devices and therefore the unique pathway to translation for medical devices needs to be addressed.

The development and licensing of medical products is overseen by the EMA in the EU. In the EU, medical products are treated as either medical devices or drugs. This activity will likely produce both categories of products and some combination products such as would be found in the materials engineering theme (there are three categories in the US), thus requiring monitoring of the full regulatory landscape to inform the research and development process as the technologies and devices are refined.

Medical devices are broadly divided into three classes, based on the level of control necessary. In the EU, strict quality systems must be complied with and, depending on the class of device, clinical trials must be performed. Academic translational research has typically resolved this complexity through establishing a quality assurance/quality regulation structure first that then facilitates the approval and running of clinical trials. The recommendation is that such a QA/QR structure is established as part of the coordinating function's remit.

LOTTIE POLLAK

Scars mark you out, sometimes in a bad way, but also in a good way.
The fear is that scarring closes doors, but actually it can open them; you just need
to let it. I don't see my scars when I look in the mirror, but I know other people do.
I know they're looking at me because I look different. Sometimes I think about what it would
be like to not be noticed. More than anything, you have to fight the temptation to shut doors.
It feels scary, but if you can do that, you, and everyone else, will always end up in a better place.
The scars belong to you. You don't belong to them.

SECTION 4: EXPERIMENTAL MEDICINE AND CLINICAL TRIALS

Experimental Medicine covers all clinical disciplines and concerns the study of patients and clinical samples to better understand disease process and develop new treatments and improved clinical outcomes. The delivery of a holistic clinical and basic scar free healing research strategy will only be possible with the inclusion of robust experimental medicine studies, in order to take discoveries from basic scientific research projects to the clinic and ultimately to bring the predicted benefits to patients.

The journey from laboratory scientific discovery to medical progress is a critical one that has many important steps and challenges. Well-designed clinical studies are the cornerstone of experimental medicine since they offer an opportunity to test scientific hypotheses in patients and advance understanding of disease. In the case of clinical trials, this may also lead to new and better treatments. With regard to tissue healing, scarring and fibrosis there are unique opportunities for experimental medicine studies because affected tissue in the skin may be available for analysis. Therefore, it is possible to directly test the effect of a new or promising treatment on the biology of the skin and explore markers of activity or improvement in response to therapy.

When a new chemical or biological compound is developed that may be useful in treatment it must pass through a series of important development stages. The first stage is to understand the likely mechanism and this may be explored in the laboratory. Animal model studies can also test effectiveness in disease models and also give important safety, toxicity and pharmacodynamics/ kinetic data. A promising potential new drug may pass into a Phase I (First in human clinical trials: FIHT for a new medicinal product) trial when they are assessed in healthy volunteers. The main aim of these studies is to establish safety and give information about the doses to test in later development.

The next stage is a Phase II clinical trial, where the new drug is compared with a control compound or placebo in a target disease. If the results are encouraging and there are no unacceptable safety concerns then the drug may move to a Phase III clinical trial. Phase III studies are robust and large and aim definitely to show clinical benefit for the new drug. Typically, at least two adequately powered positive phase III trials are needed before drug licensing authorities and regulators are approved for approval of the drug.

As well as being a slow process, drug development through these phases is very expensive. High quality basic science and laboratory studies, especially using disease models and clinical samples, may speed up the selection of new drugs for development and increase the chances of later success. Phase IV studies are normally conducted in order to build long-term safety and efficacy of medicine that have market approval.

The design of any clinical intervention as a first-in-human experiment may require short-term readouts/ outcomes, which can be linked to longer-term milestones (e.g. demonstrating a critical change in a biomarker of disease process linked to scar development or progression, or the example of dynamic cell behaviour being monitored, as described in Imperative 6).

It is imperative that any clinical trial is effectively powered (i.e. has sufficient subjects participating), in order that a clear and robust outcome is generated. The pre-existing biobanks and patient registries mean that thousands of patients already contribute to the research effort and are committed to the research mission. A well-designed engagement with our patient base will be required to recruit these individuals and others to clinical trials as existing and new subjects, and will be developed prospectively. As our knowledge of the underlying genetic and epigenetic determinants of scarring develops, it will become possible to stratify patients according to their propensity to develop scars; this will reduce the numbers required to participate in trials whilst retaining statistical robustness. Finally, the scar research community is already closely aligned with epidemiological modellers and trial design experts

(based at MRC Integrated Epidemiology Unit at Bristol University, for example), and other more flexible trial design models such as 'adaptive trial design' can be deployed to address specific issues in patient recruitment if these develop.

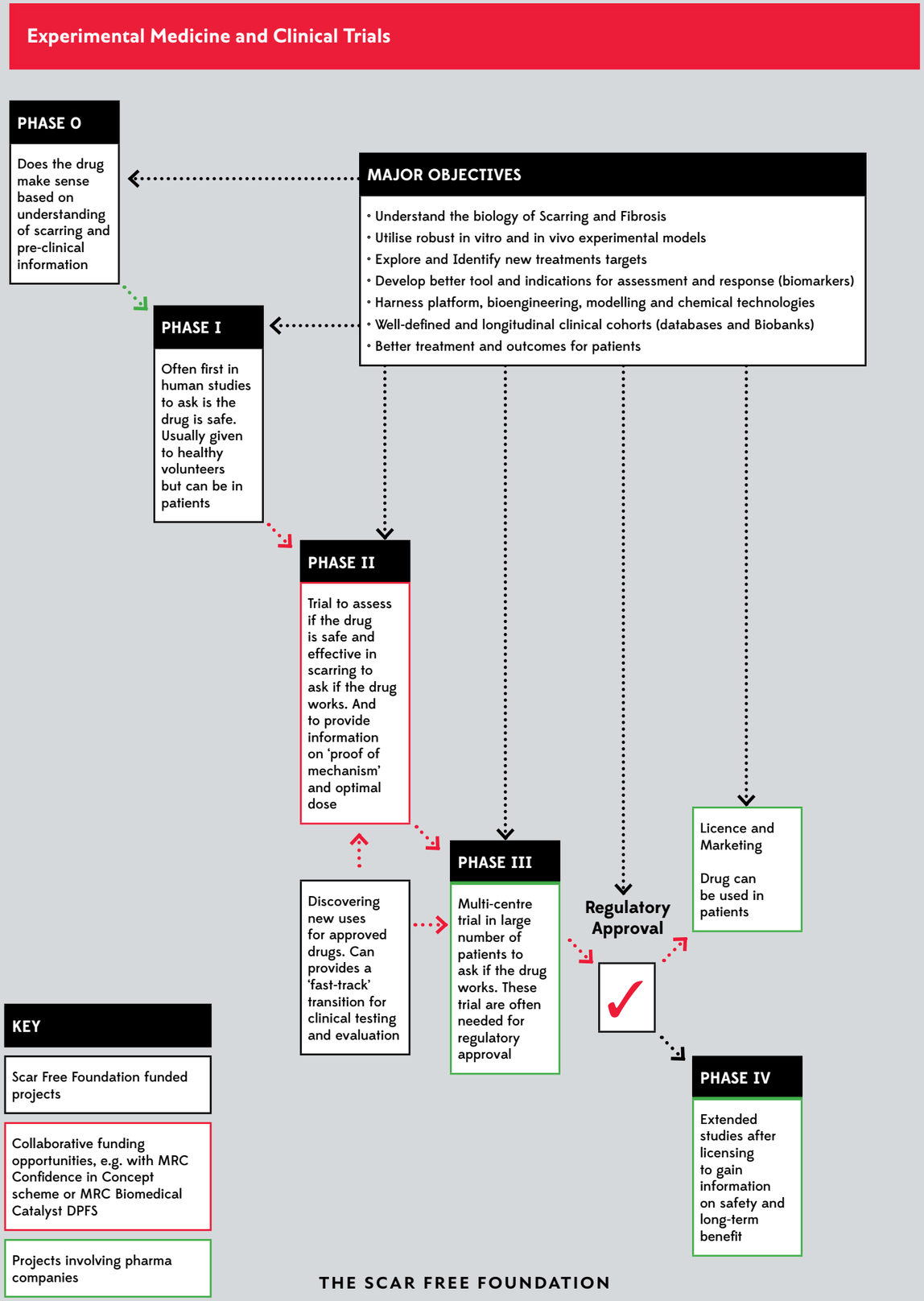
While clinical trials require large numbers of participants to produce robust data, smaller-scale experimental medicine studies can also be undertaken using fewer patients to investigate specific techniques or treatments. This is relevant for the in vitro 'skin-on-chip' models described in Imperative 8, but also for surgical techniques such as the burn model developed by Professor Dominic Furniss at the University of Oxford, used in breast reconstruction surgery. This is a short-term model, whereby tissue is burned and analysed three hours later, prior to removal from the blood supply, for histological, immunohistological and coagulatory outcomes. Studies can also be conducted with specific conditions featuring fibrosis, such as Dupuytren's disease – a benign fibromatosis of the hands and fingers that leads to flexion contractures. Both the burns model and the studies with patients with Dupuytren's disease have the advantage of easy access to superficial tissue for drug applications.

The overall goals of experimental medicine are to provide a comprehensive pathway leading to effective management and improve outcome for patient with existing scars and for new patients following injury and during the course of scarring. The major aims are to develop a portfolio of experimental initiatives in order to enhance translational medicine including:

- The testing of new candidates (e.g. Small molecules/ Biologics) and approaches to treatment (e.g. Cell Transplantation /Gene Therapies) for tissue scarring and excessive scarring conditions.
- The potential use via repurposing of existing medicines to treat scarring
- The performance and efficacy of clinical trials in an academic/NHS environment within Designated Clinical Trials Units (CTU) to combat scarring. Trials progress from first in-human studies (FIHT)/Phase I through to Phase III and approval of license.
- Collaborative efforts with Academia, the NHS and foundation trusts and with colleagues in industry to promote the drug discovery pipeline in scarring and partner in clinical trials.

Figure 2 summarises the approach to experimental medicine and clinical trials.

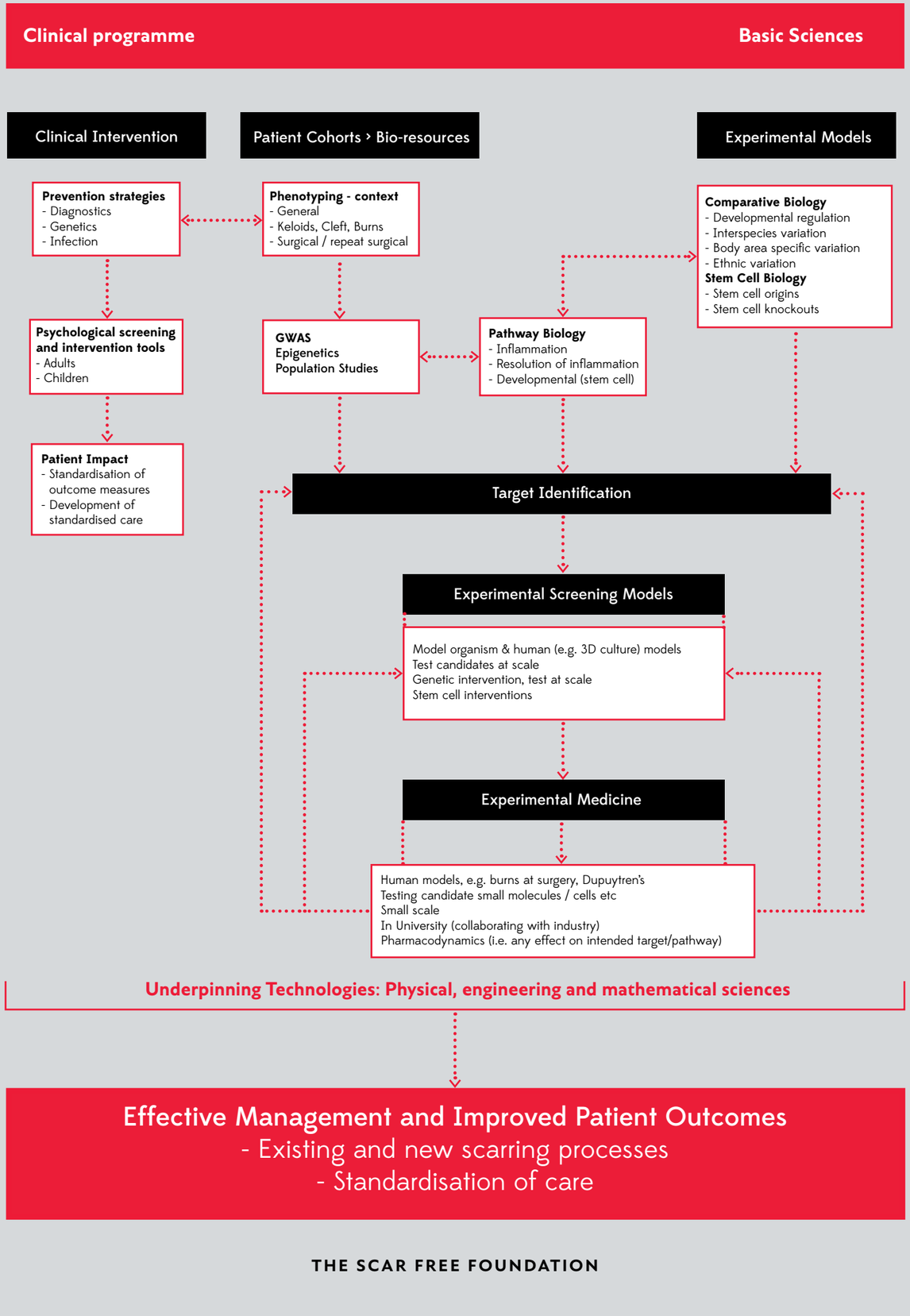
Figure 2



SECTION 5:
THE ROADMAP TO SCAR FREE HEALING

Key to the success of this strategy is the integration of imperatives, initiatives and enablers across the clinical and basic science arms of the framework. The illustration on the opposite page (Figure 3) shows how these areas come together to deliver effective management and improved outcomes in our target populations.

Figure 3



SECTION 6: ENABLERS

Successfully implementing this Scar Free Strategy will require the effective coordination of resources and oversight of initiatives, in order to ensure that funds are directed towards the most promising projects across a range of complementing scientific areas, as defined in the strategy. The following enablers are recommendations from the Scar Free Advisory Group in respect of the key priorities to facilitate delivery of the strategy. It will be the role of the Delivery Group to fully consider these recommendations and to oversee the implementation phase, in collaboration with The Scar Free Foundation's Research Council.

Infrastructure

Coordinating function

The establishment of a single Research Coordination function is a high priority, to create a UK network of scientific and clinical excellence, and to facilitate the achievement of the aims of this strategy.

This function will facilitate the implementation of the strategy and progress towards scar free healing (responsibility for which lies with The Scar Free Foundation, via its Research Council and Board of Trustees). A major requirement for the function will be that it ensures full discussion and integration of the different elements of the research programme, advises on the appropriate balance of basic sciences and clinical work and ensures integration of research and clinical programmes.

All research and clinical funding will be awarded competitively through open calls, under the direction and management of The Scar Free Foundation Research Council. A defined Patient and Public Involvement programme should also be developed to ensure that the patient voice was represented at all stages of the development, implementation and delivery of the strategy.

The recommendation is that the Coordinating function is aligned with a strong academic centre with a well-regarded clinical trials unit and the requisite infrastructure for quality assurance/quality regulation for medical devices. This would ideally sit in a leading university, capable of coordinating and directing cutting-edge basic scientific research in academic disciplines relevant to scar free healing, and with the capabilities to take therapies from the lab to the clinic via robust experimental medicine procedures. In addition, it is anticipated that a small number of other centres of excellence will act to deliver other aspects of the scientific and/or clinical strategy. The Delivery Group are asked to consider the advantages and disadvantages of this 'hub and spoke' model.

Requirements:

This will require leadership of the highest academic and managerial calibre, as well as well-qualified staff to manage processes and relationships.

The details of the resources required will be defined by the Delivery Group.

Network of collaborating centres

The recommendation is that between three and five additional centres are developed, whose focus will be on one or more aspects of the research strategy. In each case, it will be vital to show how the basic sciences research programme is coordinated with and underpins improvements in clinical care. Partnerships between universities/basic sciences institutes and hospitals will therefore be essential. It is also recommended that flexibility be retained for certain projects to be re-funded after review on project completion, in order to ensure that improvements in clinical practice reach patients effectively.

Patient and Community Involvement

The development and utilisation of defined patient cohorts of individuals with a tendency to develop scarring conditions/diseases in order to investigate intrinsic pathways, biomarkers and potential anti-scarring agents will be of fundamental importance if therapies are successfully to be taken to the clinic. This underlines the importance of a strong clinical trials capability in the coordinating function, and the necessity of promoting a culture of research recruitment into trials within clinical settings.

Bioresources

In order to achieve the goals of the Scar Free Strategy it will be necessary to have access to precisely characterised (phenotyped) biological material from thousands of individuals – a bio-resource. The recommendation is that the scar free healing coordinating function seeks to partner with, for instance, the Wellcome Trust, which runs an annual call for bio-resources, to establish a dedicated biobank facility or build on an existing facility if appropriate.

Funding

It is suggested that a certain amount of relatively low-level flexible, 'kick-start'-type funding be available to pump-prime innovative projects and collaborations that have significant potential to lead to treatments or solutions, but which may not fall into the typical categories of project receiving grant funding. Funding should also be available to encourage international partnerships and collaborations where appropriate, although this should be a UK-based initiative at its inception. The coordinating function would advise on the distribution of this funding, in accordance with direction from The Scar Free Foundation Research Council.

It is recommended that The Scar Free Foundation should develop funding relationships with UK Research Councils, industry and other charitable sources to leverage the philanthropic funding raised by the Foundation. The ability to work collaboratively with the NHS, pharmaceutical companies and other partners will enable The Scar Free Foundation to leverage not only the funds raised but also additional resources such as access to chemical compounds and biological material vital for effective studies to be undertaken.

People and Training

A scar free healing PhD programme in which students are potentially able to work across and between centres should be a high priority. The recommendation is that this programme is administered by the coordinating function, with the aim being to award multidisciplinary PhD studentships to be co-supervised by experts in different but complementary fields (such as Immunology and Bioengineering), in order to promote collaboration and working across disciplinary boundaries. Beyond the shorter-term aims of individual projects, this will enable capacity building within the fields relevant to scar free healing, and will thus be crucial in the training of future scientific leaders who will ultimately deliver the scar free agenda.

Dissemination and Sharing Best Practice

It is recommended that The Scar Free Foundation support cross-speciality networks (for example in the psychosocial and outcome development areas) in order to promote information-sharing and discussion within the research community and to facilitate efficient dissemination of research outcomes. There should ideally also be regular updates regarding current research and outputs for the wider interested community (beyond those directly involved in research and clinical practice). It is suggested an annual 'Scar Free Conference' be held. This would enable those involved in scar free research to disseminate, share good practice and develop collaborations.

Finally, the recommendation is that specific additional funding is made available for the dissemination phase of projects that report clear potential patient benefit.

LUCY WILSON

It sounds like a cliché, but living with scarring does get better, and it's good to hear that from someone. I like to think somebody out there might hear one of our stories and feel like 'I'm not the only one'. A lot of burns survivors feel like they're alone. They're not. To me, being scar free is a mind-set. I wouldn't be the person I am without my burns, they're one of the things that make me unique, and I'm proud of that. Working towards scar free healing will clearly mean huge breakthroughs in treatment, but also in attitudes. Giving people confidence, helping them accept themselves and removing any stigma; that's what I think Scar Free means.

SECTION 7: OUTPUTS, OUTCOMES AND IMPACTS

Scar free healing is expected to deliver wide-ranging impacts, in terms of the variety of conditions implicated, and significant benefits in respect of the outcomes for patients. The medical conditions in which scarring is a significant factor are manifold, and a number have been described in this strategy document. However, it is also anticipated that numerous benefits will accrue as the specific clinical and scientific aims within the strategy are investigated and achieved along the road to scar free healing.

Clinical Outputs and Outcomes

- Better understanding of the cause of conditions: including genetic factors (e.g. craniofacial conditions) and the role of psychosocial factors (e.g. in burn injury).
- Better understanding of complications: including wound infection; sepsis and inflammation; scarring (both physical and psychological); the impact of trauma; and capsular contracture.
- Better understanding of psychosocial issues: factors and processes that influence adjustment to appearance amongst young people living with visible difference; and the relationship between wound healing and psychosocial factors.
- Development of standardised: screening tools (where appropriate); diagnostic and investigation pathways; rehabilitation pathways and long term care; and outcome measures.
- Development of standardised: interventions (including psychosocial) [depends on development of standardised screening tools above].
- Networks: Creation of a supportive network of academic centres and trial facilities building large patient cohorts, and a generation of research enabled clinicians and basic scientists working together with their patients in a focused, integrated pursuit of prevention, reconstruction, rehabilitation, and psychosocial well-being.

Clinical Impacts

- Translational studies: planning and gradual implementation of a program of translational studies leading to standardisation of care across main speciality areas, as outlined above.
- Equity of care: Increased equity of care (N.B. whilst excellence of care is the ideal, equity in care based on a 'good enough' model may be more achievable).
- Centres and networks: Priming of centres and research networks that can be competitive in recruiting future major grant funding beyond the direct support of The Scar Free Foundation.

Basic Science Outputs and Outcomes

- Better understanding of the cellular and molecular mechanisms of scarring and both extrinsic and intrinsic factors that affect this process.
- An understanding of the genetic and epigenetic factors controlling the response to wounding.
- A trained generation of biomedical scientists, clinician scientists and clinicians in scarring research and treatment.
- Robust model systems for testing of novel therapeutics and devices.
- Partnerships and collaboration across the UK.
- Patient engagement with research.

Basic Science Impacts

- Treatments for patients with an existing scar (both pharmacological and cell-based treatments).
- Cell and/or device based technologies to monitor and prevent scarring.
- Validated drug targets – new and novel anti-scarring therapeutics with the ability to tailor therapies to individuals (i.e. precision medicine) to prevent scarring.
- The UK leads in scarring research and treatment.

DANIEL JACKSON

To be an object of interest can be hard to deal with.
Just raising awareness of scarring and disfigurement would be a major breakthrough.
Very often in the media, in films, on TV, disfigured or scarred people are portrayed as 'scary'.
I think it's time for that to change. Scar free to me is an incredibly powerful statement.
It says that a child might be able to undergo surgery, and then not have to feel
sad when they look in the mirror. It says that they'll be able to have the confidence
that any young child should have. I think that's a beautiful idea.

CONCLUSION

Throughout the development of the Scar Free Strategy, input and guidance has been sought from experts in the relevant scientific and clinical disciplines. The consistent feedback has been that scar free healing within a generation is an ambitious and visionary goal, but one that is achievable and realistic.

The effects of scarring are serious and often life-changing. Many patients are affected enormously, both physically and emotionally, because of their scars. It is the firm belief of The Scar Free Foundation and the Scar Free Advisory Group that this burden can be lifted – through scar free healing.

The implications are far-reaching. Scar free healing would, by definition, result in the healing of wounds without scarring – and remove the scarring element from a variety of genetic conditions. Furthermore, scars cause complications in a wide range of medical conditions, and the achievement of scar free healing would enable improvements in treatment across this spectrum of conditions.

The programme of research recommended in this strategy deals with the different areas of clinical and scientific relevance for the pursuit of scar free healing. There are quick wins, as well as more challenging goals that will nonetheless have a direct impact on the lives of people living with scars now, such as standardisation of care. There are also imperatives that will take considerable time and investment to achieve, but the unique element of this strategy is the overarching goal to bring together complementing disciplines to address the ultimate goal of scar free healing.

The Scar Free Foundation is in a unique position to nucleate and run a research and clinical programme to deliver scar free healing and the advances of recent years together with the resources of the UK's outstanding universities, pharmaceutical companies and the NHS, make the timing perfect for the pursuit of this bold ambition.

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- Mrs Rona Slator, University of Birmingham
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- Dr Amber Young, University of Bristol

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- Ms Rona Slator, Birmingham Children's Hospital
- Dr Amber Young, University of Bristol

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- Dr Mark Richardson, Smith and Nephew
- Professor Jonathan Sandy, University of Bristol
- Ms Rona Slator, Birmingham Children's Hospital
- Dr Mamta Shah, Royal Manchester Children's Hospital
- Dr Amber Young, University of Bristol

Appendix 1: Scar Free Advisory Group Membership

Professor Maggie Dallman
Deputy Chair of The Scar Free Foundation Research Council (as Chair)

Professor David Abraham
Representative from University College London

Professor Anthony Bull
Representative from Imperial College London

Dr. Alex Clarke
Clinical Lead on The Scar Free Healing Advisory Group, Visiting Professor Centre for Appearance Research UWE

Ms. Charlotte Coates
Research Manager at The Scar Free Foundation

Mr. Brendan Eley
Chief Executive of The Scar Free Foundation

Professor John Iredale
Representative from Edinburgh University and Bristol University

Professor Roger Pedersen
Representative from Cambridge University

Professor Peter Ratcliffe
Representative from Oxford University

Mr. Tim Streatfeild
Patient Representative

Mr. Anthony Wilkinson
Academic Partnerships Project Manager at Imperial College London

Appendix 2: Principal Member Organisations

Founding Principal Member:

British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS)

Principal Members:

British Association of Aesthetic Plastic Surgeons (BAAPS)

British Burn Association (BBA)

British Psychological Society (BPS)

British Society for Surgery of the Hand (BSSH)

Craniofacial Society of Great Britain & Ireland (CFSGB&I)

Appendix 3: Delivery Group

The Scar Free Foundation will constitute a 'Delivery Group' who will be charged by the Board of Trustees to advise on the implementation and delivery of the Scar Free Strategy. The group will undertake the following:

- To identify and engage appropriate expertise from the research community and seek their opinion on the funding mechanisms suggested for the delivery of the Scar Free Strategy.
- To review the recommendation of a coordinating function/role for the Scar Free Healing Strategy.
- To prepare and recommend a five year 'implementation plan' to the Board of Trustees.

It is envisaged that this group will meet up to three times during 2016 and deliver its report to the Board of Trustees in November 2016.

It is suggested the Group be comprised of individuals with the following range of skills:

- A Leader with organisational development, strategy and management skills.
- A senior Management Consultant or strategist with wide, non-research or medical related experience to bring a fresh perspective.
- A senior level Academic/Clinician with experience of the direction of a large-scale, multi-centred and multi-disciplinary research programme.
- A senior level Research Director (or recently retired Research Director) from a charity such as the British Heart Foundation, Cancer Research UK, Parkinson's or Alzheimer's Research UK.
- A Patient Representative
- The Chief Executive of The Scar Free Foundation
- A member of The Scar Free Advisory Group

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