Barriers to clinical research in Africa; a quantitative and qualitative survey of clinical researchers in 27 African countries

by

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DECLARATION

I, *Dr Aletta Conradie*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Chapter 1: Review of the Literature

1. Objectives

This review aims to explore existing healthcare literature describing factors affecting the growth of healthcare research in Africa.

2. Literature search strategy

Initial attempts at a systematic approach to the literature were abandoned when it proved impossible to identify suitable studies using MeSH terms or other keywords. Studies exploring barriers to research in Africa are limited. We proceeded by following a branching logic to assimilate suitable literature for this review.

3. Quality criteria

The reference lists of relevant articles found through a broad-range of individual topic-searches were hand-searched to create as comprehensive a review as possible. All publications relevant to the subject were obtained online, through the University of Cape Town Health Science Library. Ultimately there were 24 relevant resources were identified and their findings are discussed below.

4. Summary of the literature

4.1 Introduction

There is very little in the current literature assessing potential barriers faced by researchers embarking on research collaborations in Africa. The African environment has been labelled as non-conducive to research with outdated legislations and misaligned priorities between researchers and policy makers. [1]

The inequity in health research is epitomised by the concept of the “10/90 gap”. It is estimated that only 10% of global health research funding targets diseases affecting 90% of the population. [2] Diseases affecting large portions of humanity, notably the African continent, are underrepresented in the current literature. Global health research priorities are largely aligned with topics selected to benefit those in possession of financial and intellectual resources. [3] High income countries register over 100 times more clinical trials annually than low income countries and over 80% of the world’s low-income countries are on the African continent. [4]

The WHO further elaborates that as little as 1% of global research and development targets diseases highly prevalent in Africa, including malaria, tuberculosis and

neglected tropical diseases despite representing an overwhelming proportion of the global burden of disease. [5,6]

There is an increasing need for clinical research to be re-prioritised to align with global population health, which should be guided by burden of disease data. This is a recurring topic of concern in the literature. [2, 7 8]

4.2 Research landscape

In 2008, 46 African member states' representatives signed the Algiers Declaration at the Ministerial Conference on Research for Health in the African Region. Its target was "narrowing the knowledge gap to improve Africa's health". The need for improved research efforts was acknowledged and countries committed themselves to implementing policies to improve continental health research output. Objectives of the declaration included increased research funding, the development of national research agendas, improved collaborative efforts between nations, human resource expansion and improved training facilities. [8, 9] Despite this formal acknowledgement of the need for improved health research, Africa's contribution to global research remains sparse 10 years later.

According to the Global Research Report in 2010, all of Africa produced the same number of research publications in one year as the Netherlands. Africa contributed only 1% to global clinical medical publications between 2004 and 2008. Almost half of this research was produced by South Africa, near double the amount of publications of the runner up, Egypt, which was trailed by Tunisia, Nigeria and Morocco. [6]

Over the period 1999-2016 there was a steady increase in the number of registered trials for most WHO regions, albeit at vastly variable rates. In 2016 the Western Pacific regions had more than 20 times the number of trials registered compared to Africa.[4] According to the WHO International Clinical Trials Registry Platform (ICTRP) in 2016, the African region generated a total of 459 trials of which nearly half were produced by South Africa (197). Of note is that some Eastern Mediterranean countries (Egypt, Libya, Morocco, Tunisia, Somalia, Sudan, Djibouti) are grouped separately from the rest of Africa by the WHO regions and were not included in their African statistics. [4]

Full time equivalent health researchers (FTE) per million population is a measure of research potential and investment in research output. On average Africa has 15 FTE per million, but many countries have less than 5. The number of health researchers is

directly proportionate to countries' income levels. High income countries have on average 352 times more health researchers than low income countries. [4]

In 2015 the WHO launched the 2030 Agenda for Sustainable Development with emphasis on Sustainable Development Goals (SDGs).[5] A weakness of the now expired Millennium Development Goals which focussed on programmes targeting specific health conditions, was a lack of attention to health systems performances and service delivery. In contrast, the focus of the new SDGs is to strengthen health systems globally in order to achieve universal health coverage. One of the six main lines of action of the 2030 Agenda is scientific research.

4.3 Developing human resources for health

The massive healthcare challenges of the African continent must be overcome by overburdened, understaffed healthcare workers already losing the fight. [10] One example is the HIV/AIDS pandemic that is increasing the demand for health coverage across the continent, especially in those areas with pre-existing extreme shortages of healthcare workers. [11]

A direct correlation exists between the size of a country's health workforce and its population health; human resources are indispensable to achieve improved population health. [12] [13] A continued reality across Africa is the persistent haemmorhage of skilled health care workers seeking career opportunities in richer countries offering economic and political stability. [14] In 2006 the WHO estimated that 37% of all South African trained doctors were practicing abroad. The numbers are similar, if not as drastic, for the rest of Sub-Saharan Africa. [12]

The WHO Health Workforce report in 2015 describes the extent of the human resources shortage in Africa by highlighting that the majority of African countries have critically low physician densities less than 0.5 per 1000 population, the level the WHO estimates below which primary healthcare is not sustainable. [15] South Africa has a physician density of 0.77. The world's lowest physician density is seen in Liberia at 0.014 physicians per 1000 population. [15]

Young African researchers are demotivated by the lack of career opportunities, research funding, remuneration and lack of experienced mentorship in many regions of the continent, perpetuated by the emigration of experienced researchers seeking employment in high income countries. [17] Health worker migration contributes to the

poor research output from developing countries and perpetuates the cycle of inequality in both health research and clinical medical care. [16] Unless the importance of research funding on the continent is emphasized and promoted by governments, research capacity is unlikely to escalate. [1, 10]

Inequalities exist not only between countries but also within countries. Rural areas have comparatively fewer skilled health workers than urban areas. In Tanzania the capital, Dar-es-Salaam, has a workforce of medical officers and specialists 30 times that of its rural regions. [12]

All governments share responsibility to aim for universal health coverage for its citizens. Examples exist of successful policy implementation to improve human resources for health in Brazil, Mexico, Ghana and Thailand. [13] Through political commitment and targeted solutions Brazil managed to increase its health workforce significantly; nurses by 600% and doctors by 66% between 1990-2009. Over the same 20-year time period Ghana's investment in improving its health workforce resulted in a rapid increase in health professionals; the number of nurses increased by 260% and physicians by 1300%. The message from this editorial is clear, quick fixes will not have the desired outcome and will most likely fail. [13] Adequate funding and long-term policies with fully fledged political commitment are required to generate a skilled, motivated health workforce.

Table 1. WHO data 2006 [12]

Global data	**Americas**	**Sub-Saharan Africa**
Population	**14%**	**11%**
Burden of disease	**10%**	**25%**
Health workforce	**42%**	**3%**
Health expenditure	**>50%**	**<1%**

4.4 Insufficient access to information technology

The WHO emphasizes the need for linked, large scale digital databases in order to attain compiled global health statistics allowing for targeted healthcare initiatives. For many African countries it would require significant financial resources to shift data handling and record keeping onto a digital platform. [5]

A lack of widely available information technology is the norm in many countries across Africa with manual record keeping, poor archiving and inaccessibility to data exacerbating research difficulties. [17] Communication in healthcare is seen as an essential step to achieving an improved foundation of knowledge and inoculating a culture of research amongst healthcare workers. [14]

A survey of general research practices among African emergency medicine practitioners reports access to literature, either because of inadequate internet availability or inadequate access to literature databases, as a prominent barrier to research involvement. Nearly half indicated frequently being blocked from accessing literature due to subscription charges. Other significant barriers uncovered were a lack of research-related funding, dedicated research time and training opportunities. The lack of experienced research supervisors across Africa was also emphasized. Over 80% of respondents recognised the importance of research both in critical thinking and education, but felt that more training was needed to help them apply research to clinical practice. The majority agreed that insufficient emergency care research was being conducted in Africa. [18]

The WHO Health Inter Network Access to Research Initiative (HINARI) addresses the problem of access to research by providing online access to a number of full text journals to many LMIC's. [17] However, internet access remains a problem for many in Africa despite rapid growth of the industry locally and globally. The average internet penetration in Africa is 28,3%, but is less than 10% in many countries. The rest of the world averages 54%, with most first world countries exceeding 80% internet availability. There are also marked inequities within Africa in this regard. Kenya boasts the highest internet penetration with 81,8% and Eritrea the lowest with a mere 1,3%. [19] These numbers refer to internet availability only with many African internet services on offer notoriously sporadic and unreliable.[20]

4.5 Regulatory bodies

Ethics review committees (ERCs) serve as the gatekeepers to research involving human participants and are considered the cornerstone of ethical research. Without a competent, functional human research ethics committee structured health research is not feasible. [21] There is a marked lack of experienced, structured ethics boards in many African countries. When present, these are often understaffed and ill equipped to handle the intricacies of large scale research collaborations. Failure of ERCs leads to compromised population health by delayed processing, wrongful rejection, or inadequate approval of research protocols.

A 2009 survey evaluating ERCs across 18 Sub-Saharan African countries showed that most institutions had an ERC of some description with huge variation in their composition. ERC members listed a lack of resources and inadequate training as barriers to fulfilling their roles. An astonishing 92% of committees reported being inadequately trained to perform their duties effectively. Of ERC members 38% had no formal training whatsoever. Despite the availability of a multitude of e-learning resources in this field, only 4% of respondents reported having utilised this. Whether as a result of ignorance or lack of access was not clear. None of the respondents had electronic data systems in place and relied on outdated paper-based systems. [21] Addressing these shortcomings has been considered a matter of urgency for some time. [1 21 17]

4.6 Global efforts to promote research

Globalisation refers to the increasing interconnectedness of populations and the shift in traditional boundaries to unite larger populations through shared humanitarian goals. In healthcare, globalisation is a powerful tool to target issues which transcend boundaries and are often best solved through collaborative efforts. [2] In 2012 United Nations General Assembly emphasized the need to urgently accelerate the transition towards universal, affordable, quality health services. [13] A critical step toward achieving global health is addressing the health needs of the poor, a massive task to which many believe health research may hold the key. [3]

Global health partnerships and collaborative research efforts have great potential to improve healthcare across the globe, especially in Africa and other developing nations. Despite the mutually beneficial outcomes for research funders as well as local

researchers, a potential exists for exploitation and power imbalance within these complex relationships. It is essential for African collaborators to assume partnership roles in international projects to produce high quality research addressing health issues relevant to local populations rather than simply facilitating first world research. [10] [3] The ethical complexities of collaborative research are discussed by Emanuel et al., however this topic extends beyond the scope of this paper. [22]

4.7 Collaboration to bridge the gap

Collaborative research is one method to bridge the 10/90 gap, which epitomises the inequalities in health research. [2] Collaborations can be intra- or trans-continental with pooling of resources enabling research to be conducted effectively on a larger scale. The benefit of shifting boundaries in research is evident in the increase in power through large numbers of patients recruited in multicentre, multinational settings. [23]

To understand and address the issues related to collaborative research on the African continent it is important to evaluate regional demographics. The African continent consists of 54 independent countries. The United Nations geo-scheme divides Africa into 5 sub-regions: North, South, East, West and Central. UNESCO estimates that 2000 languages are spoken among the continent's 1,11 billion inhabitants. Nigeria alone has 250 languages.

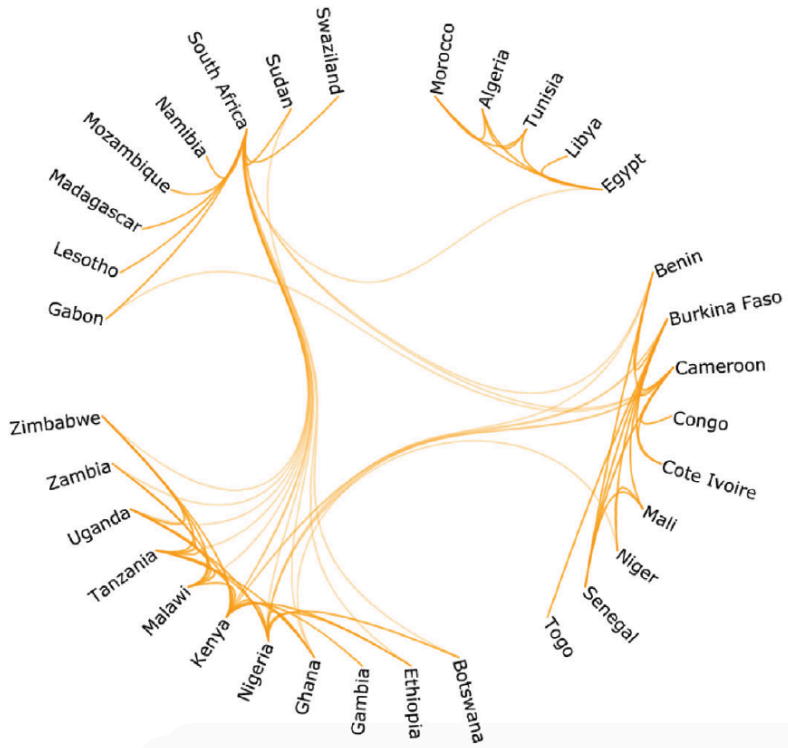
Tremendous cultural, religious and geographic separation exists between the different African sub-regions. Two important barriers to collaboration between African countries are the difference in language and culture[6] Linguistic divisions which stem from colonialist influence in the 19th century, are an important barrier to meaningful research collaborations in the African academic environment and have traditionally prevented the creation of taskforces to address shared health issues. [17]

Anglophone (South- and West Africa), Francophone (West- and Central Africa), Portuguese (West- and South Africa) and Arabophone (North Africa) countries have research links to other countries of similar linguistic backgrounds. [6] The thin research thread between the African sub-continents is largely reliant on research forerunners South Africa, Kenya, Nigeria and Egypt venturing outside of traditional confines. [6]

Figure 1. Network of collaboration in Africa [6]

NETWORK OF COLLABORATION:

A new visual interpretation of collaboration, by paper not by number of researchers, reveals clusters of countries with the strongest partnerships.



Source: *Web of Science*[SM]: Analysis: Daniel Hook[v]

Divisions in international collaborations also exist, with North Africa having strong links to France with 42% of publications in Algeria being co-authored by French researchers. Egypt has strong cultural ties to Saudi Arabia, which co-authors approximately 6% of its research. The USA, UK and Germany have the largest share of overall collaboration with Africa. Together these three research giants have authorship in 50% of annual global research publications. [6]

4.8 Regional initiatives

There are some success stories in the promotion of research on the continent, mainly through smaller scale regional group initiatives. National Health Research Systems are identified by the WHO as an essential component in modern health systems. Their function is to provide governance and support, both financial and other, to ensure a thriving research milieu. These have been found to be lacking across large parts of the African continent due to lack of funding, qualified human resources and research development strategies. [17]

In 1998 in response to the need for improved health research collaborations in the West African region, the Western African Health Organisation (WAHO) was created. Its mandate was to use collaborative research to address shared concerns and improve health systems in the region. [17] The framework used to implement this change was adapted from Pang et al's steps to strengthening health research systems that include stewardship, financing, creating and sustaining resources, and producing and using research. [24] An additional component, partnership, was added after its central importance was realised in the region. Each component was targeted by the WAHO research development program.

Stewardship in many countries needed to be addressed, specifically the lack of national policies regarding research guidance and training. An important target was the weakness of ethics committees in member states. Regional training programmes and other resources were made available. An online resource database was established to assist researchers in the region. Financial aid was provided to facilitate priority research projects. Under the heading of resource creation, the WAHO facilitated individual and institutional capacities in the form of scholarships and collaboration opportunities. The programme produced research published both in printed journals and presented at conferences.

In collaboration with research partners in and beyond the region, $3 million was invested in the activities targeting the framework. They conclude by saying that many of the activities would not have been possible without joint funding from ECOWAS member states. [17]

5. Conclusion

The development of LMIC's is especially closely linked to health research. [1] Health research creates an opportunity for policy makers to identify and prioritise health issues and subsequently take appropriate action. Health research creates a link between the health needs of populations and those in a position of authority. [3] Only once joint action is taken to address the challenges faced by researchers in Africa can research standards be raised to international levels. [1]

Communication in healthcare is seen as an essential step to achieving an improved foundation of knowledge and inoculating a culture of research amongst healthcare workers. [14] However, suitable information technology, especially internet access, is

unavailable to many health researchers. Addressing this barrier would potentially facilitate research participation and improve research output.

Collaborative research on the continent is one way to improve research output and create a joint taskforce to target shared health concerns. Encouraging researchers to join local, national and global research networks could reduce isolation and initiate collaborations in similar projects. [16] Regional group initiatives such as ECOWAS have been shown to be effective in promoting research partnerships and increasing joint research output.

The ASOS study represents a new opportunity to tap a large and diverse network of clinicians that have collaborated across the continent to collect data in a new field. The lived experience of these clinician-researchers represents an important mine of data that may be used to facilitate future studies.

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Title Page

Barriers to clinical research in Africa; a quantitative and qualitative survey of clinical researchers in 27 African countries

Running title: Barriers to clinical research in Africa

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Summary (Abstract)

Background

There is a need for high quality research to improve perioperative patient care in Africa. The aim of this study was to understand the particular barriers to clinical research in this environment.

Methods

Electronic survey of African Surgical Outcomes Study (ASOS) investigators, including 29 quantitative Likert scale questions and eight qualitative questions with subsequent thematic analysis. Protocol compliant and non-compliant countries were compared according to the WHO statistics for research and development, health workforce data and world internet statistics.

Results

Responses were received from 134/418 invited researchers in 24/25 (96%) participating countries, and three non-participating countries. Barriers included the lack of a dedicated research team (47.7%), reliable internet access (32.6%), staff skilled in research (31.8%) and team commitment (23.8%). Protocol compliant countries had significantly more physicians per 1000 population (4 vs 0.9 $p<0.01$), internet penetration (38% vs 28% $p=0.01$) and published clinical trials (1461 vs 208 $p<0.01$) compared to non-compliant countries. Facilitators of research included establishing a research culture (86.9%), simple data collection tools (80%) and ASOS team interaction (77.9%). Most participants are interested in future research (93.8%). Qualitative data reiterated human resource, financial resource, and regulatory barriers. However, the desire to contribute to an African collaboration producing relevant data to improve patient outcomes, was expressed strongly by the ASOS investigators.

Conclusions

Barriers to successful participation in ASOS related to resource limitations and not the motivation of clinician investigators. Practical solutions to individual barriers may increase the success of multi-centre perioperative research in Africa.

Keywords

Africa, Biomedical Research, Research Personnel, Surveys and Questionnaires

Introduction

It is estimated that approximately 95% of Africans, or 1.1 billion people, do not have access to safe and affordable surgery.[1] Perioperative research is therefore urgently needed to guide improvements in delivery of this essential service.[2] However, African researchers contributed only 1% to global clinical medical publications between 2004 and 2008 and nearly half thereof were produced by South Africa.[3] The African environment has been labeled as non-conducive to research,[4] yet many of these challenges have not been explored in the literature.

Through an improved understanding of the African research environment, the potential of international collaborative research to develop healthcare may be better harnessed.[4, 5]

The African Surgical Outcomes Study (ASOS)[2] (ClinicalTrials.gov NCT03044899) was a large, multinational African collaborative study. Using the International Surgical Outcomes Study (ISOS) methodology,[6] perioperative outcomes were assessed in 25 African countries. The ASOS National Leaders accepted an agreement with the ASOS principal investigators to provide country data from a minimum of 10 surgical centres, and data on > 90% of the eligible patients for every participating hospital. However, despite this formal agreement, only 11/25 countries (44%) fulfilled the protocol data requirements. It appears that these requirements were overly demanding for the African research environment. In addition, some countries failed to participate in ASOS despite prior national leader agreements to do so.

The reasons for country non-participation in ASOS, and the protocol data non-compliance are unknown. Our hypothesis is that there were important barriers to research participation and protocol compliance in ASOS. The aims of this study were to quantify and describe; i) the barriers and, ii) facilitators of research participation encountered by ASOS investigators, and to iii) determine factors which would ensure future research participation in Africa.

To the best of our knowledge, no other surveys have evaluated the challenges of conducting perioperative research in Africa. Even outside the African environment, there exists a paucity in the global biomedical literature on the theme of challenges in research participation.

Methods

Project Organisation

This study was approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee on 8 November 2016 (HREC REF: 799/2016).

Data Collection

This survey was developed through a literature review of the African research environment and factors previously identified internationally to be associated with research productivity. As the literature was sparse, we proposed potential barriers through our experience conducting ASOS. In order to identify other previously unrecognised barriers, we specifically allowed for free-text responses. The survey was not piloted. The digital survey was distributed in English and French to 418 researchers originally approached for participation in ASOS. All participants provided explicit informed consent. Twenty-nine questions with 5-point Likert scales were used to quantitatively evaluate possible barriers and facilitators to research in Africa as informed by the ASOS experience. Eight free-text questions offered opportunities for elaboration and were evaluated qualitatively. The survey is in the supplementary appendix. Data collection was conducted between 29 November 2016 and 2 April 2017 with weekly email reminders to non-responders. Safe Surgery South Africa (SSSA) hosted the Research Electronic Data Capture System (REDCap)[7] platform and coordinated electronic distribution and data monitoring. Access to data was limited to the investigators and platform administrator. The investigators were blinded to the respondents, but the platform administrator was unblinded to facilitate survey follow-up.

Statistical Analysis

Quantitative responses were graded on a Likert scale. We created a dichotomous variable to present the overall agreement with each statement, by amalgamating ‘agree’ and ‘strongly agree’; and amalgamating ‘neutral’, ‘disagree’ and ‘strongly disagree’. Categorical variables were described as proportions and compared using chi-square tests, Fisher’s exact tests, and Pearson’s chi-square tests, as appropriate. Continuous variables were described as mean and standard deviation if normally distributed or median and interquartile range (IQR) if non-normally distributed. Comparisons of continuous variables between groups were performed using unpaired

t-tests or Mann Whitney U-tests as appropriate. The 95% confidence intervals (CI) are reported for the quantitative data.

The ASOS protocol compliant and non-compliant country data were compared according to the World Health Organisation (WHO) statistics for research and development,[8] the WHO global health workforce data,[9] and world internet statistics.[10]

All free-text responses were analysed thematically. Two investigators (A.C. and R.D) worked independently to familiarise themselves with the data-set before initial coding. Coded data were analysed inductively to extract initial themes. Through consensus, initial themes were refined and collated to create a coherent description of the central message of the data. The emergent themes from the thematic analysis were then integrated with the proposed themes identified by the ASOS authors that had already been examined in the quantitative questions of the survey. This produced a richer understanding of the barriers and facilitators that were already suggested, but also identified and explored several new themes not previously identified. By consensus, representative extracts from the data were selected for inclusion in the report.

We have not reported the country of origin of data to protect the identity of our respondents.

Results

A total of 184 (44.0%) responses (137 English and 47 French) were received from the 418 researchers originally invited to participate in ASOS, of which 134 of 184 (72.8%) consented to participation in the study (Figure 1). Responses were received from 27 countries, including 24/25 (96%) of the participating ASOS countries and three non-participating countries (Botswana, Gabon, Rwanda). Responses were received from 10/11 (90.9%) protocol compliant countries and 14/14 (100%) of the non-compliant countries (Figure 2). Two respondents omitted their country identification data. The number of responses per country is shown in Supplementary Figure 1.

There was a significant difference between ASOS-protocol compliant and non-compliant countries with respect to physician density per 1000 population[9] (4 vs 0.9 $p<0.01$), internet penetration[10] (38% vs 28% $p=0.01$) and published clinical trials between 1999 and 2016[8] (1461 vs 208 $p<0.01$). The density of skilled healthcare workers in compliant as well as non-compliant countries (16.3 vs 16.6 respectively, $p>0.05$) is well below the WHO critical threshold of 22.8 per 10 000 population required to provide adequate primary healthcare.

Barriers to research participation

The barriers to research are shown in Table 1 (Supplementary Table 1). The three most common barriers were a lack of 'human resources', 'financial constraints' and 'data collection'.

1. Human Resources. Human resource problems were the most frequently cited barrier to research (Table 1), with 84/134 (62.7%) of respondents experiencing at least one human resource related barrier. Team member-related factors frequently cited included the absence of a dedicated research team 61/128 (47.7%), the lack of staff skilled in research activities 41/129 (31.8%) and team commitment 31/130 (23.8%). Inadequate research team leadership was also an important barrier 31/130 (23.8%). Clinical duties and workload, and unskilled colleagues were minor barriers.

These findings were supported by themes in the qualitative data describing poor team cooperation, lack of overall support and a feeling of isolation in conducting research activities.

2. Financial constraints. The 'financial barriers' to research related either to the 'resources' needed to conduct clinical research or, to a lesser degree, 'compensation' for research activities. Limited or unreliable internet access was the most frequently cited resource limitation in the quantitative questions (42/129 (32.6%)) and this was supported by the free text responses.

Research was considered costly by some respondents, however the overwhelming majority (118/128 (92.2%)) indicated being willing to participate in similar unfunded research in future. There was little consensus about what would constitute a reasonable fee for participation amongst those that felt compensation was required.

3. Data collection. Data submission was found to be difficult by a small number of respondents. Free text responses revealed that poor record-keeping and difficult access to records contributed to the difficult logistics around data collection.

4. Regulatory requirements. A minority of respondents indicated experiencing difficulties with regulatory requirements, either at a national or hospital level. Respondents from two of the three non-participating countries indicated having had national regulatory approval problems. Patient consent was not an important barrier during ASOS. Earlier and improved communication with regulatory bodies at a national and hospital level was recommended by some to ensure future participation.

While most respondents indicated that regulatory requirements were not a barrier to participation in ASOS, free-text responses revealed that for some it was an absolute barrier. Furthermore, a new regulatory barrier emerged through qualitative assessment that some ethics boards require payment for their services, which deterred some respondents from participating in unfunded research like ASOS.

5. Other barriers. Language as a barrier to participation was reported by 19/129 (14.7%) respondents of which 18/19 (94.7%) were from French or Arabic speaking countries. Statistically language was a greater barrier for participants from non-compliant countries compared to compliant countries (8 vs 10 $p<0.01$).

A small minority of researchers indicated that the experience was so demanding that they would not be interested in future participation or indicated that this type of research was not valuable. Only 4/130 (3.1%) believed ASOS would not make a difference. Challenges related to geographical location and political unrest during

recruitment were also mentioned, as well as difficulties in getting colleagues to contribute.

Facilitation of research

The qualitative and quantitative themes describing facilitators of research during ASOS are listed below. (Table 2 for dichotomous outcomes, Supplementary Table 2 for comprehensive outcomes)

1. Contributing to an African research collaboration. The desire to contribute to collaborative African research was the most prominent facilitator in both quantitative and qualitative data sets, with 106/122 (86.9%) indicating that the goal to establish a research culture served as motivation. Free-text responses reinforced the perceived need for locally relevant data.

2. Improving patient outcomes. This theme emerged strongly from free text responses. That researchers were contributing to overcoming challenges and improving patient outcomes served as motivation during ASOS. Further, researchers were committed to using evidence to encourage authorities to take appropriate action.

3. Data collection process. Most researchers considered the data collection process to be a facilitator of the research process, with what was considered simple-to-use data submission tools (96/120 (80%)). Interaction with the ASOS team served as a motivator for 95/122 (77.9%).

4. Personal development. An emerging facilitation theme was the personal development and research network growth that occurred through involvement in ASOS. Sentiments of gratitude were expressed towards the ASOS principal investigators for their facilitation and support.

Future participation

The majority of participants (120/128, 93.8%) indicated that they would be interested in future research participation, with 118/128 (92.2%) willing to participate in future unfunded research similar to ASOS (Table 3). However, themes in the free-text responses reinforced the message that access to improved communication, logistical and monetary support, and improved training of researchers would help guarantee future participation.

Examples of typical free text responses to barriers, facilitators and future participation are shown in Table 4.

Discussion

Principal findings

As the largest African surgical multinational collaboration to date, ASOS provided a unique opportunity for understanding clinical research in this challenging environment. While clinical providers should be considered separate to researchers, in ASOS the majority of the researchers where clinicians, and so these findings are relevant to clinician-researchers in Africa. Barriers to research included the lack of a dedicated research team, unreliable internet access, a lack of staff skilled in research activities and poor team commitment. Our research suggests that the absence of a skilled research team is perhaps the most important barrier to collaborative research participation in Africa. A lack of adequate resources necessary to conduct clinical research was the second most important barrier to research. More than one third of respondents did not have reliable internet access necessary for data capturing during ASOS. Available resources and productivity differed between protocol compliant and non-compliant countries, with a significantly higher physician density, internet penetration and absolute volume of published clinical trials in the protocol compliant countries. Language was a significant barrier for participants from non-compliant countries, specifically those from Francophone and Arabophone origins.

A desire to establish a research culture, the use of simple data collection tools and interaction with the ASOS research team were considered facilitators of collaborative research. African clinician researchers are committed to collaborative research answering context-specific questions about African outcomes.

Strengths and weaknesses of the study

There is limited literature on barriers to clinical research in Africa, with a single peer-reviewed multinational survey conducted in the African environment. This survey evaluated the attitudes and practices towards research in emergency medicine, of which 77.4% were practicing in Africa.[11] The most prominent barrier listed was lack of research funding (64.3%). Other barriers included a lack of training opportunities, research time and research culture. Only 64.3% listed clinical work as their main duty, which differs fundamentally from our survey, where almost all ASOS researchers were clinicians. Importantly, 80% of the respondents agreed that they need to be shown how to use research to improve clinical practice. Our study differs in that it provides

data from a diverse group of clinician researchers across a range of medical disciplines in Africa.

There were limitations to our study. Despite multiple reminders our completed survey response rate was 32% with the majority of countries yielding only a few responses. Limited resources may have contributed to the low response rate. Protocol compliant countries had a greater representation than non-compliant countries, which may reflect the better resource availability including internet accessibility. We therefore do not clearly understand the limitations to research in the ASOS non-compliant countries, and in other African countries which did not participate in ASOS. Future research into the African research environment should aim for improved continental coverage, specifically including those regions that did not participate in ASOS.

Relevance of the study

Health research is considered a key component of achieving universal global health[12], yet global health research priorities are largely determined by those in possession of financial and intellectual resources.[13] High income countries register over 100 times more clinical trials annually than low income countries.[8] There is an urgent need for clinical research priorities to be re-aligned with global population health needs as reflected by worldwide burden of disease data.[14-16]

These data provide some information on how to improve success in clinical research in Africa in the future.

Research personnel

Many African countries have critically low densities of physicians and skilled healthcare workers. Despite 25% of the global burden of disease, Sub-Saharan Africa has less than 1% of global financial health resources and 3% of the global health workforce.[17] Health researchers in developing countries are poorly paid,[18] and young researchers are often demotivated by the lack of career opportunities.[19] Health worker migration contributes to the poor research output from developing countries and perpetuates the cycle of inequality in both health research and clinical medical care.[12, 18, 20] Unless the importance of research on the continent is emphasized and supported by governments and other funders, research capacity is unlikely to escalate.[4, 5, 21]

Research support functions

The WHO emphasizes the need for linked, large scale digital databases in order to attain compiled global health statistics allowing for targeted healthcare initiatives.[22] However, essential research tools like computers, printers and notably internet access are not commonplace in many centres across the continent with manual record keeping, poor archiving and inaccessible data exacerbating research difficulties.[19, 23] The average internet penetration in Africa is 28.3% but is less than 10% in many countries.[10] In this environment any form of research, especially large-scale collaborative research like ASOS, is exceptionally challenging. Funding allocated to essential resources such as standard office resources and internet access could improve research output on the continent.

Research leadership

Experienced mentors are needed to continue building an African research culture,[19] where a lack of research leadership was expressed by nearly one in four respondents. Investing in the development of African research leaders is a potential long-term strategy for increased research participation.

Regulatory requirements

Regulatory requirements are reported as a major barrier to clinical research in Africa. Without a competent, functional, human research ethics committee, structured health research is not feasible.[24-26] A 2009 survey evaluating ethics review committees (ERC) across 18 Sub-Saharan African countries showed that most institutions had an ERC of some description with huge variation in their composition. Of these members 38% reported never having had any formal training.[24]

Regulatory difficulties compromising research were infrequently cited in our survey. The observational nature of ASOS with a waiver of consent in most centres may explain this finding. However, our study suggested that there was an inadequate access to ethics committees in some regions, which may further threaten research participation, together with the requirement of some ethics committees for payments for review of investigator-initiated and led research. We are concerned about the potential conflict of interest implied in the monetary requirements for ethics approval.

Success stories

There have been some success stories in the promotion of research, largely through small regional group initiatives.[19, 27] Collaborative research on the continent is one way to bridge the 10/90 gap by improving research output through the creation of joint taskforces to target shared health concerns.[12, 14] Global health partnerships and collaborative research efforts also have great potential to improve healthcare in Africa and across the globe.[18, 28] It is important that collaborative efforts are universally standardized, yet sufficiently pragmatic to ensure efficient, clinically important research in a resource constrained environment.[29]

Conclusions

There was an acknowledgement of the importance of context specific African research to improve patient outcomes. Barriers do exist, but researchers are committed to collaborating on future projects, and experience a personal and professional fulfilment and growth through research participation. We believe that population health in developing countries can be improved through the promotion of health research, global research priority alignment and targeted health resource allocation.

Details of authors contributions

Design of the original survey: R.D., B.B.

Design of the protocol and first draft of manuscript: A.C.

Quantitative analyses: B.B., A.C.

Qualitative analyses: R.D., A.C.

Review of writing: B.B., R.D.

French translations of survey and qualitative data: P.F.

Contribution to the manuscript: All authors.

Acknowledgements

We thank all ASOS participants for their part in uncovering the unique set of challenges faced by researchers on the continent.

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Dawid van Straaten of SSSA for design and administration of the REDCap platform.

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Chivaugn Gordon for her critical appraisal of our qualitative data.

Declaration of interests

B.B.: Principal investigator of ASOS

A.C.: MMed degree purposes

Funding

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Tables and figures for publication

Table 1. Barriers to participation in African Surgical Outcomes Study (ASOS). Data presented as n/N (%, 95% CI).

	Agree and strongly agree	**Neutral, disagree and strongly disagree**
We do not have a research team	61/128 (47.7, 39.0-56.3)	67/128 (52.3, 43.7-61.0)
We do not have reliable internet access	41/129 (31.8, 23.7-39.8)	88/ 129 (68.2, 60.2-76.3)
We have too few skilled staff for research	41/129 (31.8, 23.7-39.8)	88/129 (68.2, 60.2-76.3)
My team was not committed	31/130 (23.8, 16.5-31.2)	99/130 (76.2, 68.8-83.5)
There is lack of research leadership in my institution	31/130 (23.8, 16.5-31.2)	99/130 (76.2, 68.8-83.5)
Research is too expensive	31/127 (24.4, 16.9-31.9)	96/127 (75.6, 68.8-83.5)
Language used for communication made participation difficult	19/129 (14.7, 8.6-20.8)	110/129 (85.3, 79.2-91.4)
ASOS demanded too much of my time	18/129 (14.0, 8.0-19.9)	111/129 (86.0, 80.1-92.0)
My colleagues are too unskilled to do this type of research	16/130 (12.3, 6.7-18.0)	114/130 (87.7, 82.0-93.4)
Lack of recognition for participation in ASOS	15/130 (11.5, 6.1-17.0)	115/130 (88.5, 83.0-94.0)
My focus is on providing clinical care, not research	15/129 (11.6, 6.1-17.2)	114/129 (88.4, 82.8-94.0)

Hospital regulatory approval requirements made participation difficult	14/130 (10.8, 5.4-16.1)	116/130 (89.2, 84.0-94.6)	
National regulatory approval requirements made participation difficult	11/130 (8.5, 3.7-13.3)	119/130 (91.5, 86.8-96.3)	
I am not senior enough	5/130 (3.8, 0.5-7.2)	125/130 (96.2, 92.8-99.5)	
I don't believe this type of research is valuable	5/130 (3.8, 0.5-7.2)	125/130 (96.2, 92.8-99.5)	
I don't believe ASOS will make a difference	4/130 (3.0, 0.1-6.0)	126/130 (97.0, 94.0-99.9)	

Table 2. Facilitators for participation in African Surgical Outcomes Study (ASOS). Data presented as % (95% CI).

	Agree and strongly agree	**Neutral, disagree and strongly disagree**
I want to establish a culture of research in my hospital and this motivated me to participate	106/122 (86.9, 80.9-92.9)	16/122 (13.1, 7.1-19.1)
The data submission tools for ASOS were simple which motivated me	96/120 (80.0, 72.8-87.2)	24/120 (20.0, 12.8-27.2)
Interaction with ASOS researchers motivated me to participate	95/122 (22.1, 70.5-85.2)	27/122 (22.1, 14.8-29.5)

Table 3. Future participation. Data presented as n (%).

	Yes	**No**
Would you like to participate in similar research in future?	120 (93.8)	8 (6.3)
Can your hospital participate in future unfunded studies?	118 (92.2)	10 (7.8)
Did you find your participation in ASOS valuable?	117 (95.9)	5 (4)
Were there any issues related to patient consent or participation?	6 (5)	114 (95)

Table 4. Examples of typical free text responses to barriers, facilitators and future participation.

Barriers	
Human resources	*"I had no support with conducting this research from the surgeons at my hospital and other staff. I was met with disinterest and sometimes hostility from doctor and nursing colleagues which has made me not want to do research at my hospital in future." – Protocol compliant country* *"Not many willing hands to help." – Protocol non-compliant country*
Financial barriers **Resources**	*"No office space or computer access at work to capture data. I was forced to capture list of the data after hours on my personal computer." – Protocol compliant country* *"People didn't come through with data collected as they had no money to print and upload the data and data collection sheets." – Protocol non-compliant country* *"Some remote areas had no internet [which made] data uploading difficult." – Protocol non-compliant country*
Compensation	*"The vast majority of my colleagues expected a salary for this work. It was difficult to explain [to] them that it was basically interesting for our hospital to participate in an international study." – Protocol compliant country* *"Due to lack of monetary rewards, many hospitals leaders withdrew from the study." – Protocol compliant country* *"[We would expect] $25-50/day for data collectors." – Protocol non-compliant country*

	"[We would expect] $1500 as motivation for those who will collect the data" – Protocol compliant country
Data collection	*"The competing clinical duties and poor hospital record keeping made data collection a challenge." – Protocol compliant country* *"Our people spent many hours driving to hospitals and in wards and records looking for folders." – Protocol compliant country*
Regulatory requirements	*"[There was] no clear regulatory body in my country to get approval from for (this) research." – Protocol non-compliant country* *"We often have to pay for local and national ethical review boards which costs $600 for each study. This can limit our participation." – Protocol compliant country*
Other barriers	*"Some of the cases booked that week could not be done due to strike action [so data could not be collected]." – Protocol compliant country* *"[This] made me realize that it is far too much work to try and get other people to contribute." – Protocol compliant country*
Facilitators	
Contributing to an African research collaboration	*"It was a big African study. I wanted to be part of it." – Protocol compliant country* *"I was longing to find a group of people of like mind to collaborate with in my area of interest and ASOS opened the door." – Protocol non-compliant country* *"The European scores are taught and applied in our population. But this is not always valid. These are different populations. We should generate African data." – Protocol non-compliant country*

	"Only Africans can tell the African story." – Protocol compliant country
Improving patient outcomes	*"There is so little interest from government to change the perioperative situation for patients. Pressure from publications like ASOS might raise awareness." – Protocol compliant country* *"I believe these kind of outcome studies are essential to addressing poor outcomes in surgery in Africa. I am very motivated to participate because I think this kind of research will help us focus efforts for improvement in surgical care." – Protocol non-compliant country* *"I think we have an ethical responsibility to improve best practice, and this can only be done by finding honest answers to challenging clinical questions." – Protocol compliant country*
Personal development	*"Working for ASOS gave me an opportunity to learn how to overcome the many barriers that come along with research work." – Protocol non-compliant country* *"[Participating in ASOS] helped us in realising we can establish a research team at the hospital." – Protocol compliant country* *"[Participation in ASOS] showed us that meaningful, international quality research can be done at our institution" – Protocol compliant country* *"[Participation in ASOS] has sharpened my interest and skills in research/ data collection. It has served as eye opener to the possibilities and benefits of interdisciplinary and multinational based research." – Protocol compliant country*
Future participation	
Targets to facilitate future participation	*"To reinforce the communication with a better and faster web connection." – Protocol compliant country*

	“Provide resources for internet.” – Protocol non-compliant country *“To help us to establish a communication system/web connection, and work tools like a computer.” – Protocol compliant country* *“I needed a workshop for orientation of Hospital Leaders.” – Protocol non-compliant country*

Figure 1. Participation in the African research survey. Data presented as n (%).

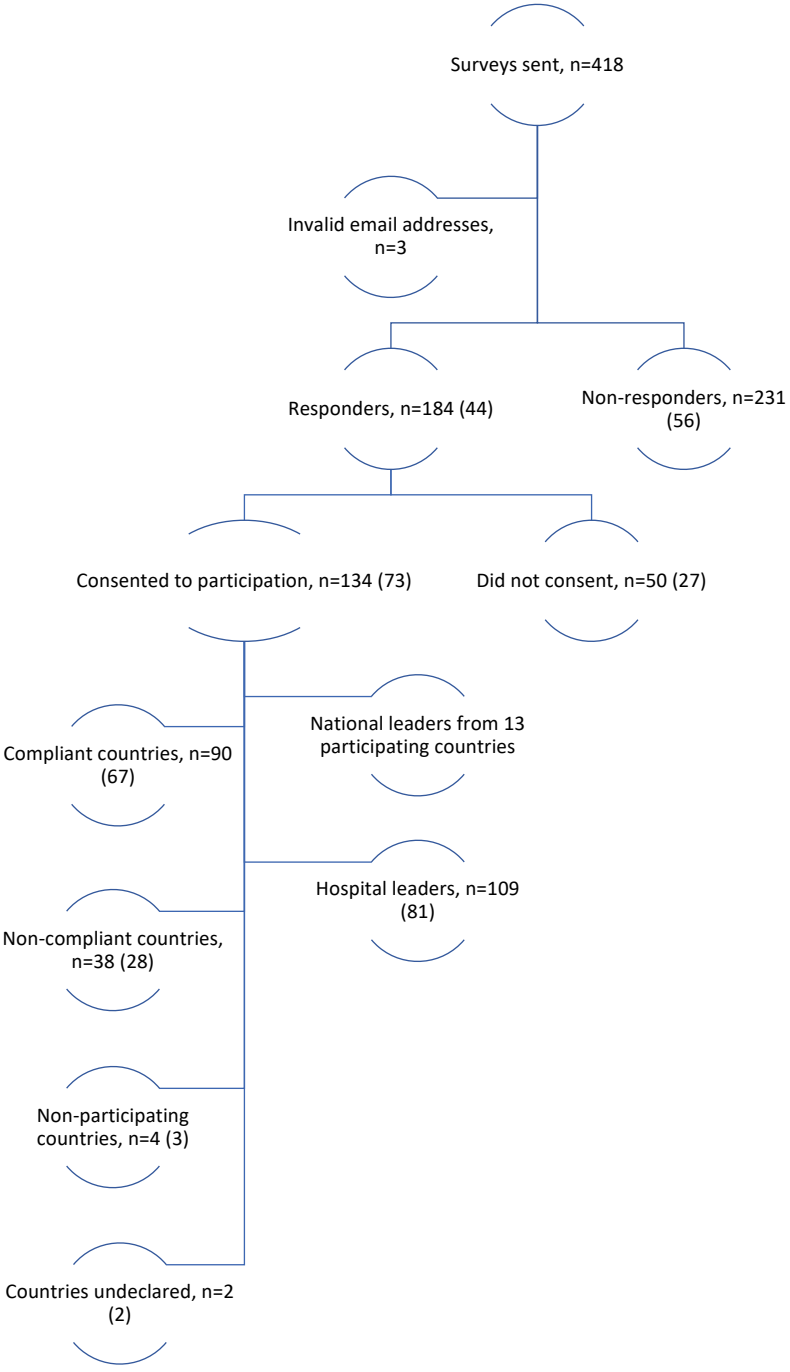
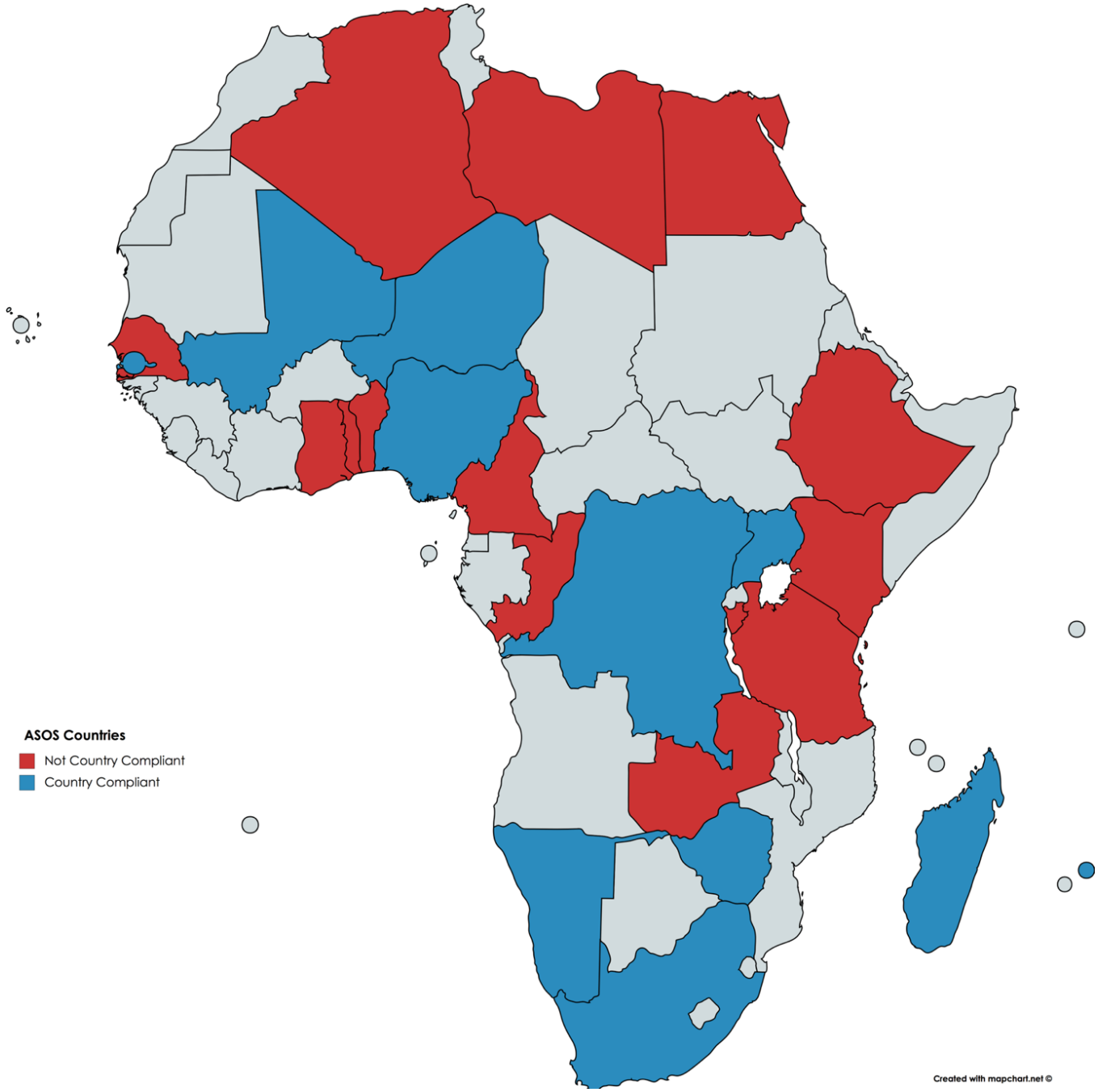
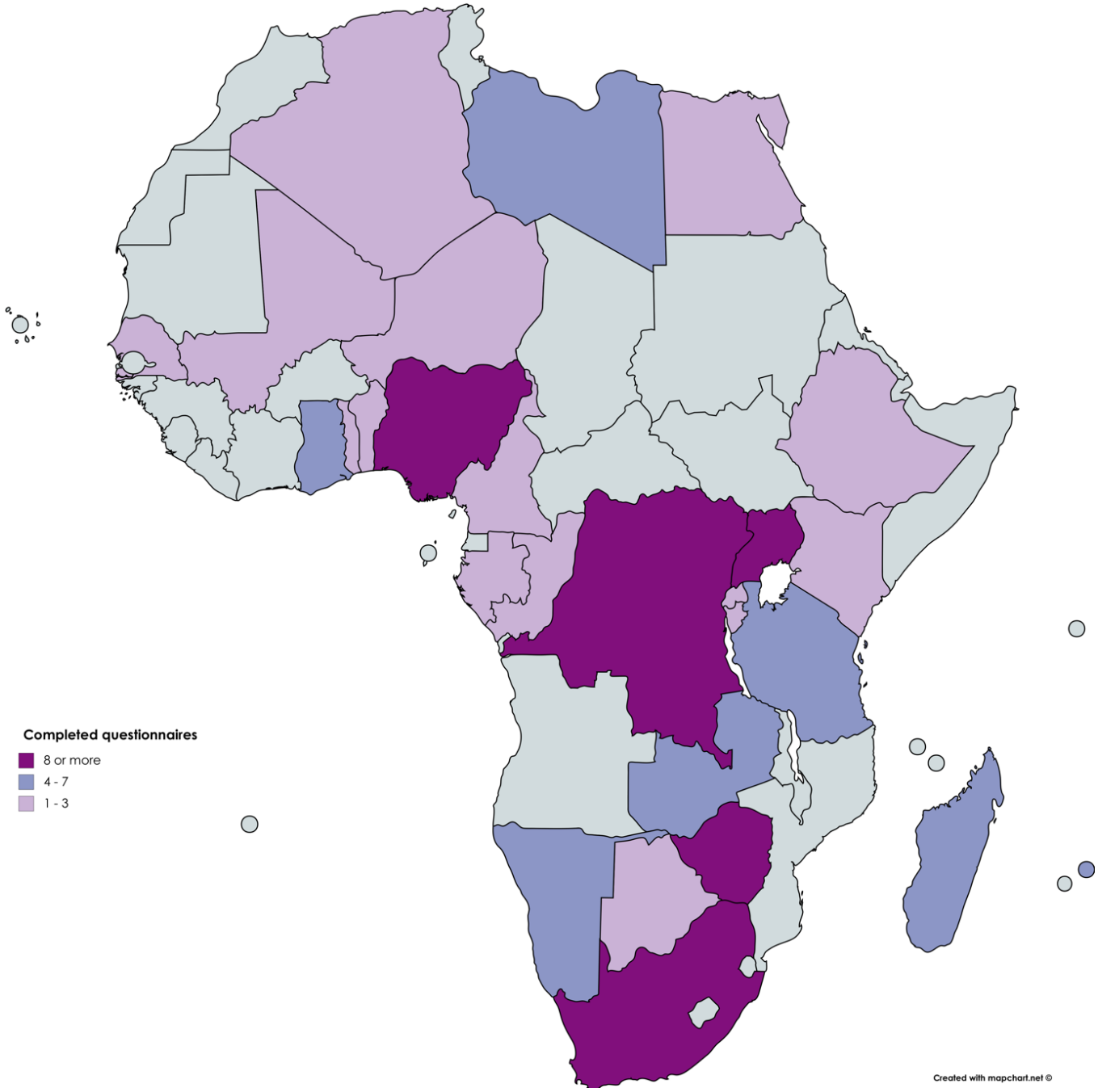


Figure 2. ASOS Countries protocol compliance



Supplementary documentation

Supplementary Figure 1. Survey responses by country



Supplementary Table 1. Barriers to participation in African Surgical Outcomes Study (ASOS). Data presented as n (%).

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
We do not have a research team	17 (13.3)	44 (34.4)	20 (15.6)	27 (21.1)	20 (15.6)
We do not have reliable internet access	13 (10)	28 (21.7)	19 (14.7)	33 (25.6)	36 (27.9)
We have too few skilled staff for research	14 (10.9)	27 (20.9)	19 (14.7)	40 (31)	29 (22.5)
My team was not committed	10 (7.7)	21 (16.2)	13 (10.0)	48 (36.9)	38 (29.2)
There is lack of research leadership in my institution	12 (9.2)	19 (14.6)	16 (12.3)	40 (30.8)	43 (33.1)
Research is too expensive	11 (8.7)	20 (15.7)	17 (13.4)	41 (32.3)	38 (29.9)
Language used for communication made participation difficult	5 (3.9)	14 (10.8)	5 (3.8)	41 (31.5)	64 (49.2)
ASOS demanded too much of my time	5 (3.8)	13 (10.1)	15 (11.6)	63 (48.8)	33 (25.6)
My colleagues are too unskilled to do this type of research	5 (3.8)	11 (8.5)	14 (10.8)	46 (35.4)	54 (41.5)

Lack of recognition for participation in ASOS	2 (1.5)	13 (10.0)	19 (14.6)	48 (36.9)	48 (36.9)
My focus is on providing clinical care, not research	2 (1.6)	13 (10.1)	6 (4.7)	53 (41.1)	55 (42.6)
Hospital regulatory approval requirements made participation difficult	2 (1.5)	12 (9.2)	12 (9.2)	49 (37.7)	55 (42.3)
National regulatory approval requirements made participation difficult	3 (2.3)	8 (6.2)	15 (11.5)	54 (41.5)	50 (38.5)
I am not senior enough	2 (1.5)	3 (2.3)	4 (3.1)	40 (30.8)	81 (62.3)
I don't believe this type of research is valuable	1 (0.8)	4 (3.1)	3 (2.3)	34 (26.2)	88 (67.7)
I don't believe ASOS will make a difference	-	4 (3.1)	7 (5.4)	44 (33.8)	75 (57.7)

Supplementary Table 2. Facilitators for participation in African Surgical Outcomes Study (ASOS). Data presented as n (%).

	Strongly agree	**Agree**	**Neutral**	**Disagree**	**Strongly disagree**
I want to establish a culture of research in my hospital and this motivated me to participate	65 (53.3)	41 (33.6)	13 (10.7)	1 (0.8)	2 (1.6)
The data submission tools for ASOS were simple which motivated me	35 (29.2)	61 (50.8)	13 (10.7)	10 (8.3)	1(0.8)
Interaction with ASOS researchers motivated me to participate	37 (30.3)	58 (47.5)	21 (17.2)	3 (2.5)	3 (2.5)

Chapter 3

Appendix 1 – HREC approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 November 2016

HREC REF: 799/2016

Prof B Biccard
Department of Anaesthesia & Perioperative Medicine
D23
NGSH

Dear Prof Biccard

PROJECT TITLE: ASOS: AFRICAN SURGICAL OUTCOMES STUDY: QUESTIONNAIRE FOR THE ASOS PRINCIPAL INVESTIGATORS: (sub-study of the ASOS DATA (R004/2016)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 NOVEMBER 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Appendix 2 – Survey

Confidential

ASOS Investigators Survey

Dear Colleagues

Thank you for your participation in the African Surgical Outcomes Study (ASOS). In order for us to better understand what you found easy and difficult in participating in ASOS, we would request that you help complete this survey.

This survey will help us understand what worked or what didn't work with the ASOS study. We would like to understand what helped you participate and collect data for ASOS, and what aspects you found difficult with the study at your site.

Your participation in this ASOS survey is voluntary. By selecting the agree button for the survey, you are providing consent to complete the survey. Your responses are confidential and all data is stored in a password protected electronic format. Should you have any enquiries please contact Prof Bruce Biccard on +27 (0)21 4045442. Should you have any questions about your rights regarding this survey, you can contact the Human Research Ethics Committee at the University of Cape Town on +27 (0)21 406 6338.

We thank you for considering participation in this survey. It is hoped that the information from this survey, may improve future collaborative research in Africa.

Yours faithfully
Bruce Biccard

Background information

Do you agree to participate in this survey of ASOS?

- ◯ Yes
- ◯ No

What was your role is ASOS?

- ☐ National Leader
- ☐ Hospital Leader

Confidential

In which country did you work in ASOS?

- ◯ Algeria
- ◯ Angola
- ◯ Benin
- ◯ Botswana
- ◯ Burkina Faso
- ◯ Burundi
- ◯ Cameroon
- ◯ Canary Islands
- ◯ Cape Verde
- ◯ Central African Republic
- ◯ Chad
- ◯ Comoros
- ◯ Congo
- ◯ Cote d Ivoire
- ◯ Democratic Republic of the Congo
- ◯ Djibouti
- ◯ Egypt
- ◯ Equatorial Guinea
- ◯ Eritrea
- ◯ Ethiopia
- ◯ Gabon
- ◯ Gambia
- ◯ Ghana
- ◯ Guinea
- ◯ Guinea-Bissau
- ◯ Kenya
- ◯ Lesotho
- ◯ Liberia
- ◯ Libya
- ◯ Madagascar
- ◯ Madeira
- ◯ Malawi
- ◯ Mali
- ◯ Mauritania
- ◯ Mauritius
- ◯ Mayotte
- ◯ Melilla
- ◯ Morocco
- ◯ Mozambique
- ◯ Namibia
- ◯ Niger
- ◯ Nigeria
- ◯ Reunion
- ◯ Rwanda
- ◯ Saint Helena
- ◯ Sao Tome and Principe
- ◯ Senegal
- ◯ Seychelles
- ◯ Sierra Leone
- ◯ Somalia
- ◯ South Africa
- ◯ Sudan
- ◯ Swaziland
- ◯ Tanzania
- ◯ Togo
- ◯ Tunisia
- ◯ Uganda
- ◯ Zambia
- ◯ Zimbabwe

Did your country/ hospital recruit patients in ASOS?

- ◯ Yes
- ◯ No

Confidential

What was your role in the ASOS study in the Hospital where you worked? _____

Did your country achieve the predetermined number of hospitals required for ASOS participation?
◯ Yes
◯ No

Did your hospital enter the predetermined number of > 90% of eligible patients for ASOS into the ASOS database?
◯ Yes
◯ No

Barriers to participation in ASOS

In this section we'd like to find out what made participation in the ASOS trial difficult i.e. what you would consider barriers to participation.

Please answer how you felt the following factors made your participation in the ASOS trial difficult

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
The language used for communication related to the study and data collection tools made participation in the study difficult	○	○	○	○	○
I am not senior enough for my colleagues to follow my leadership and this made participation in the study difficult	○	○	○	○	○
My team was not committed to this type of research and this made participation in the study difficult	○	○	○	○	○
There was a lack of recognition for my participation in ASOS and this made participation in the study difficult	○	○	○	○	○
I don't believe in the value of this type of research and this made participation in the study difficult	○	○	○	○	○
ASOS demanded too much of my time and this made participation in the study difficult	○	○	○	○	○
My focus is on providing healthcare for my patients (and not research) and this made participation in the study difficult	○	○	○	○	○
I don't believe ASOS will make a difference to healthcare and this made participation in the study difficult	○	○	○	○	○

The hospital regulatory approval requirements made participation in the study difficult	○	○	○	○	○
The national regulatory approval requirements made participation in the study difficult	○	○	○	○	○
My colleagues are too unskilled to do this type of research and this made participation in the study difficult	○	○	○	○	○
There is a lack of leadership for research in my institution and this made participation in the study difficult	○	○	○	○	○

Please describe any further limitations or challenges that you faced in conducting the research for ASOS.

_____

Resources as a barrier to participation

Please answer how you felt that a lack of the following resources made your participation in the ASOS trial difficult

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
We have too few skilled staff for research	○	○	○	○	○
The research is too expensive	○	○	○	○	○
We do not have reliable internet access to conduct the research	○	○	○	○	○
We do not have a research team	○	○	○	○	○

Please describe any further limitations or challenges with resources that you faced in conducting the research for ASOS.

_____

Confidential

Factors which facilitated participation in ASOS

Please answer how you felt that the following factors made participation in the ASOS study easier (or facilitated participation in the ASOS study

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
Interaction with ASOS researchers motivated me to participate	○	○	○	○	○
The data submission tools for ASOS were simple which motivated me to participate	○	○	○	○	○
I want to establish a culture of research in my hospital and this motivated me to participate	○	○	○	○	○

Please describe any factors which facilitated your participation in the research for ASOS.

_____

Questions about participation in similar research projects in the future

Did you find your participation in ASOS valuable?
○ Yes
○ No

Why?

_____

Would you like to participate in similar research in the future?
○ Yes
○ No

Why?

_____

Were there any issues related to patient consent or participation which will make participation in similar research difficult in the future?
○ Yes
○ No

If 'Yes', please can you explain these.

_____

Can your hospital or institute, participate in future unfunded studies such as ASOS?
○ Yes
○ No

If 'No', please explain how much money would be needed for participation, and what it would be used for?

_____

What could the Principal Investigator of ASOS change to ensure your participation in future collaborative research studies?

_____

Appendix 3 – SRQR Checklist

Standards for Reporting Qualitative Research (SRQR)*

http://www.equator-network.org/reporting-guidelines/srqr/

Page/line no(s).

Title and abstract

Title - Concise description of the nature and topic of the study Identifying the study as qualitative or indicating the approach (e.g., ethnography, grounded theory) or data collection methods (e.g., interview, focus group) is recommended	Page 1
Abstract - Summary of key elements of the study using the abstract format of the intended publication; typically includes background, purpose, methods, results, and conclusions	Page 2, 3

Introduction

Problem formulation - Description and significance of the problem/phenomenon studied; review of relevant theory and empirical work; problem statement	Page 4
Purpose or research question - Purpose of the study and specific objectives or questions	Page 4, 5

Methods

Qualitative approach and research paradigm - Qualitative approach (e.g., ethnography, grounded theory, case study, phenomenology, narrative research) and guiding theory if appropriate; identifying the research paradigm (e.g.,	Page 5

postpositivist, constructivist/ interpretivist) is also recommended; rationale**	
Researcher characteristics and reflexivity - Researchers' characteristics that may influence the research, including personal attributes, qualifications/experience, relationship with participants, assumptions, and/or presuppositions; potential or actual interaction between researchers' characteristics and the research questions, approach, methods, results, and/or transferability	N/A
Context - Setting/site and salient contextual factors; rationale**	Page 5
Sampling strategy - How and why research participants, documents, or events were selected; criteria for deciding when no further sampling was necessary (e.g., sampling saturation); rationale**	Page 5
Ethical issues pertaining to human subjects - Documentation of approval by an appropriate ethics review board and participant consent, or explanation for lack thereof; other confidentiality and data security issues	See Appendix 1
Data collection methods - Types of data collected; details of data collection procedures including (as appropriate) start and stop dates of data collection and analysis, iterative process, triangulation of sources/methods, and modification of procedures in response to evolving study findings; rationale**	Page 5, 6
Data collection instruments and technologies - Description of instruments (e.g., interview guides, questionnaires) and devices (e.g., audio recorders) used for	Page 5, 6 See Appendix 2

data collection; if/how the instrument(s) changed over the course of the study	
Units of study - Number and relevant characteristics of participants, documents, or events included in the study; level of participation (could be reported in results)	Page 5, 6 See Figure 1
Data processing - Methods for processing data prior to and during analysis, including transcription, data entry, data management and security, verification of data integrity, data coding, and anonymization/de-identification of excerpts	Page 5, 6
Data analysis - Process by which inferences, themes, etc., were identified and developed, including the researchers involved in data analysis; usually references a specific paradigm or approach; rationale**	Page 5, 6
Techniques to enhance trustworthiness - Techniques to enhance trustworthiness and credibility of data analysis (e.g., member checking, audit trail, triangulation); rationale**	Page 6 Thematic analysis

Results/findings

Synthesis and interpretation - Main findings (e.g., interpretations, inferences, and themes); might include development of a theory or model, or integration with prior research or theory	Page 7 - 13
Links to empirical data - Evidence (e.g., quotes, field notes, text excerpts, photographs) to substantiate analytic findings	Page 7 – 13 (Quotations)

Discussion

Integration with prior work, implications, transferability, and contribution(s) to the field - Short summary of main findings; explanation of how findings and conclusions connect to, support, elaborate on, or challenge conclusions of earlier scholarship; discussion of scope of application/generalizability; identification of unique contribution(s) to scholarship in a discipline or field	Page 14 - 17
Limitations - Trustworthiness and limitations of findings	Page 14

Other

Conflicts of interest - Potential sources of influence or perceived influence on study conduct and conclusions; how these were managed	Page 20 (N/A)
Funding - Sources of funding and other support; role of funders in data collection, interpretation, and reporting	Page 21 (N/A)

*The authors created the SRQR by searching the literature to identify guidelines, reporting standards, and critical appraisal criteria for qualitative research; reviewing the reference lists of retrieved sources; and contacting experts to gain feedback. The SRQR aims to improve the transparency of all aspects of qualitative research by providing clear standards for reporting qualitative research.

**The rationale should briefly discuss the justification for choosing that theory, approach, method, or technique rather than other options available, the assumptions and limitations implicit in those choices, and how those choices influence study conclusions and transferability. As appropriate, the rationale for several items might be discussed together.

Reference:

O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. **Standards for reporting qualitative research: a synthesis of recommendations.** *Academic Medicine*, Vol. 89, No. 9 / Sept 2014

DOI: 10.1097/ACM.0000000000000388

Appendix 4 – British Journal of Anaesthesia (BJA) instructions to authors

Available from: https://academic.oup.com/bja/pages/Instructions_To_Authors

Instructions to authors
This is a revised version of the Extended Guide to Contributors which appeared in the Journal in 1998. It is intended to advise all contributors on the preparation of manuscripts, particularly those who are preparing a manuscript for the first time.

Please note that the journal now encourages authors to complete their copyright licence to publish form online.

IMPORTANT ANNOUNCEMENT - BJA e-Letters

New Author Submission processes and presentation

With the launch of the new Oxford Academic pages for the BJA we are putting in place new processes for submission and display of content previously known as eLetters and Out of the Blue eLetters.

See below in the author instructions or click here to find full information on how to submit Comments (previously known as eLetters) related to already published BJA articles. To view already published comments go to the Comments button associated with each article in the left-hand menu on the article page.

See below in the author instructions or click here to find full information on how to submit Correspondence (previously known as Out of the Blue eLetters). To view already published Correspondence please go to the supplementary e-Letter issues in each year, where all previous Out of the Blue eLetters are gathered. See here for an example.

SUBMISSION OF MANUSCRIPTS

Manuscripts for the British Journal of Anaesthesia should be submitted online. Once you have prepared your manuscript according to the instructions below please visit the online submission web site. Instructions on submitting your manuscript online can be viewed here.

All editorial communications should be addressed to: Professor Hugh Hemmings, Weill Cornell Medical College, New York, USA; E-mail
AIMS OF THE JOURNAL

The British Journal of Anaesthesia publishes original work in all branches of anaesthesia, critical care and pain management including the application of basic sciences, clinical practice, equipment and training. In addition, the journal publishes review articles, case reports and special articles of general interest.

PLAGIARISM

The Editors of British Journal of Anaesthesia reserve the right to use plagiarism detection software on any submitted material. For further details, please refer to the section on British Journal of Anaesthesia Policies.

CrossCheck

MANUSCRIPTS

For guidance, the requested size for articles is:

Clinical investigations: up to 3000 words and 30-40 references, 4-6 tables or figures.

Laboratory investigations: up to 3000 words and 30-40 references, 4-6 tables or figures.

Review Articles: up to 5000 words and 150 references with 4-6 figures or tables. The unstructured Summary should give a clear indication of the objectives and findings.

Narrative reviews: these should cover all aspects of a subject and avoid being 'opinion' based. Narrative reviews should follow a logical structure but not in the Introduction, Methods, Results, Discussion format. The unstructured Summary should give a clear indication of the objectives and findings.

Editorials: up to 2500 words and 25 references, 1 table or figure.

Special Articles: articles such as guidelines, history, education, surveys etc. that do not fit one of the other article types. Approval from the Editorial Office is required prior to submission. Special Articles are up to 4000 words and 150 references with up to four figures/tables, and include an unstructured Summary up to 250 words.

Case Reports: up to 1500 words and 15 references, 1 table or figure.

Correspondence: up to 1000 words and five references.

Submissions which ignore this guidance on word count or number of figures/tables may be returned without being assessed. Authors wishing to submit manuscripts with figures/tables in excess of the recommended number should justify this in the submission letter.

For review articles and laboratory/clinical investigations it is possible to include supplementary data (such as additional references for a review, expanded tables of results or additional images for investigations) for on-line publication only. Authors should make clear in their submission letter which files are to be considered for on-line only publication.

CASE REPORTS

The British Journal of Anaesthesia welcomes case reports that illustrate new approaches to established clinical problems or describing a new problem. However, the acceptance rate for case reports is considerably lower than that for clinical studies. To be of value appropriate for publication a case report must provide a significant learning point for other anaesthetists. As a simple rule, just because a case is clinically challenging does not mean that it is appropriate to publish as a case report. To give an example, a case with a difficult airway and congenital heart disease who is managed using a recognized technique for a difficult airway and a recognized approach to managing the congenital heart defect, while being a clinical challenge, does not contain any learning points. Authors are referred to the editorial (British Journal of Anaesthesia 2008; 100 (6): 744) for further background to this subject.

The British Journal of Anaesthesia requires that permission is obtained from the patient or patient's relatives for submission of the case report for potential publication. This must be obtained before submission of the manuscript and the authors must state this in their submission letter. If photographs of the patient, in any form, are used a specific signed permission from the patient must be obtained and a copy of this submitted with the manuscript. Failure to comply with this will result in rejection of the manuscript.
REVIEW ARTICLES

The British Journal of Anaesthesia welcomes review articles on clinical and scientific subjects. Authors are advised to contact the editor-in-chief before preparing or submitting a review to ascertain the appropriateness of the subject for the journal and to prevent duplication of reviews which have been commissioned or published recently.
Reviews can be either narrative or systematic (see N. Webster; British Journal of Anaesthesia 2008; 100: 285-7).

Narrative reviews should cover all aspects of a subject and avoid being 'opinion' based. Narrative reviews should follow a logical structure but not in the Introduction, Methods, Results, Discussion format. The Summary should not be structured but should give a clear indication of the objectives and findings.

Systematic reviews can be presented in the Introduction, Methods, Results, Discussion format and with a structured Summary. The subject must be clearly defined. The objective of a systematic review should be to produce an evidence-based conclusion and if there are only few RCTs available (example only 3 small studies including a total of 120 patients) the value of the review will be very limited as the level of evidence is inadequate. The Methods should give a clear indication of the literature search strategy, data extraction, grading of evidence and analysis. (Example Evans, Lysakowski and Tramer British Journal of Anaesthesia 2008; 101: 610-7).

Co-publication of Cochrane reviews in the BJA

The BJA will publish reviews already published in the Cochrane Library if they meet the editorial standards. A condition for accepting co-publication of Cochrane reviews is that the publication has been accepted by the hosting Cochrane Review Group. The manuscript has to

be rewritten to fit the BJA style and size limit of 5000 words. It is emphasized that results and conclusions of the review cannot be changed. The introduction must state that this is a co-publication of a Cochrane Review. The following should also be included:
1. The article title must end with the text 'a Cochrane Systematic Review'.
2. A footnote with the following text: '†This review is an abridged version of a Cochrane Review previously published in the Cochrane Database of Systematic Reviews xxxx, Issue xx, DOI: xxx (seewww.thecochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerge sand in response to feedback, and Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.'

PREPARING YOUR MANUSCRIPT

The standard layout of a manuscript is:

- Title page
- Summary, including Keywords
- Introduction (not headed)
- Methods
- Results
- Discussion
- Details of authors contributions
- Acknowledgements
- Declaration of interests
- Funding
- List of references
- Tables (including legends to tables)
- Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page one, etc. Start each section on a separate page.

TITLE PAGE

A separate page which includes the title of the paper. Titles should provide a reasonable indication of the contents of the paper. This is important as some search engines use the title for searches. Therefore, it is best to avoid enigmatic or vague titles such as 'An unusual cause of hypotension'. Titles in the form of a question, such as 'Is propofol epileptogenic?' may be acceptable.

The title page should include the name(s) and address(es) of all author(s). It should be made clear which address refers to which author. Details of the authors' qualifications and post (e.g., consultant, senior lecturer) are not required. An author's present address, if it differs from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript numbers (1 2 3 etc.) If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

All authors should follow the criteria for ‘authorship’ as determined by International Committee of Medical Journal Editors. For details, please refer to section on British Journal of Anaesthesia Policies.

A short running title containing not more than 50 characters (including spaces) should be included.

SUMMARY (ABSTRACT)

The Summary (Abstract) will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all Clinical Investigations and Laboratory Investigations. For Reviews and Case Reports, the Abstract should not be structured.

The Abstract should give a succinct account of the study or contents, in up to 250 words. The Results section should contain data. It is important that the results and conclusion given in the Abstract are the same as in the whole article, as the Abstract may be used, as it stands, by abstracting journals. References are not included in this section.

KEYWORDS

Three to five keywords should be included on the summary page under the heading Keywords. They should be in alphabetical order and must be classified according to MESH keywords. These can be found here . Please note that UK English spelling will be used for these. Please do not simply list words you think are key. For example, propofol should be listed as: anaesthetics i.v., propofol;

TRIAL REGISTRY NUMBER

For Clinical Trials (also see below), please include the trial registry number under a separate heading after Keywords.

INTRODUCTION

The recommended structure for this section is;

- Background to the subject
- What is known / unknown about it
- What bit you are interested in / hypothesis
- Aim of your study

As a rule, the introduction to a paper should not require more than about 200 words and have a maximum of 1.5 pages double-spaced. The introduction should give a concise account of the background of the problem and the object of the investigation. It should state what is known of the problem to be studied at the time the study was started. Previous work should be quoted here but only if it has direct bearing on the present problem. For example, a description and evaluation of an analgesic infusion as part of an intravenous anaesthesia regimen need not include an exhaustive account of the previous literature addressing the problems of intravenous anaesthesia and the many studies of different analgesics, etc.

The final paragraph should clearly state the primary and, if applicable, secondary aims of the study.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.
METHODS

The Methods section should give a clear but concise description of the process of the study. Subjects covered in this should include:

- Ethics approval / licence
- Patient population
- Inclusion / exclusion criteria
- Conduct of the study
- Data handling
- Statistics
- (CTA)

Ethics approval / licence
Regardless of the country of origin, all clinical investigators describing human research must abide by the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, and adopted in October 2000 by the World Medical Association. This document can be found at http://www.wma.net/en/30publications/10policies/b3/. Investigators are encouraged to read and follow the Declaration of Helsinki. Clinical studies that do not meet the Declaration of Helsinki criteria will be denied peer review. If published research is subsequently found to be non-compliant it will be withdrawn or retracted.

On the basis of the Declaration of Helsinki, the British Journal of Anaesthesia requires that all manuscripts reporting clinical research state in the first paragraph of the Methods section that:

- The study was approved by the appropriate Ethics authority.
- Written informed consent was obtained from all subjects, a legal surrogate, or the parents or legal guardians for minor subjects, or that the requirement for written informed consent was waived by the ethics committee.

Human subjects should not be identifiable. Do not disclose patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information. Keep copies of ethics approval and written informed consents. In unusual circumstances the editors may request blinded copies of these documents to address questions about ethics approval and study conduct.

This section must include the Clinical Trials Authorization as all studies must be registered, as per the EU directive on clinical trials which came into force on 1st May 2004. There are a number of trial registration sites including EudraCT (http://eudract.emea.europa.eu) From January 2009 studies published in the British Journal of Anaesthesia must include the trial registration number in the Methods.
Example; The study was approved by the X regional research ethics committee (Ref: 07/A123/456) and registered with EudraCT (ref: 2007:123456:AA).
For more details about Clinical Trials, please see section below.

The title of this section should be 'Methods'. 'Materials and methods' or 'Patients and methods' should not be used. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). The manufacturer's town and country must be provided. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

DRUGS

When a drug is first mentioned, it should be given by the international non-proprietary name, followed by the chemical formula in parentheses if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter). A figure giving the molecular configuration of the drug is necessary only in the case of the earliest reports of a new drug. The author should indicate in an accompanying note to the editor the source from which he has obtained the molecular configuration; it is an important requirement that the author should check the accuracy of the configuration in every detail. Drug dosages are normally given by the name of the drug followed by the dose (e.g. propofol 2.5 mg kg -1). Do not confuse drug dose with concentration.

MULTIPLE PUBLICATIONS OF HUMAN OR ANIMAL TRIALS

In the interest of minimizing the risk to human and animal subjects, as well as promoting efficient use of scarce research funds, investigators will sometimes pose several questions and make multiple measurements in a single study, with the intent of publishing multiple manuscripts. This may be a laudable practice, or it may be an inappropriate attempt to slice a single study into 'minimum publishable units'. Division of data from a single research study into multiple manuscripts is acceptable, provided three requirements are met:

1. The cover letter for every paper derived from the study explains the need for dividing the study into multiple manuscripts. This applies even if only one of the submissions is to the British Journal of Anaesthesia . It is essential that the cover letter states that other parts of the study are currently under consideration or in press with another journal. The Journal will consider the appropriateness of the division as part of the review process.

2. In all manuscripts after the first, the investigator must disclose that the subjects reported in the study have been previously reported, with appropriate citation to the first

manuscript. This practice is essential for scientific continuity. For example, should a question arise about the conduct of the study in one manuscript, readers should be able to identify all manuscripts based on the same experimental data.

3. Measurements must not interfere with each other. Such interference may happen in ways that are not evident at the time of the study. For example, measurements of pain thresholds may make it impossible to measure sedative effects. The potential for interfering measurements may not be evident if the pain thresholds and sedation effects are reported in separate manuscripts that are not appropriately cross-referenced.

PATIENTS

Data on the mean age (range), weight, sex, height, criteria for selection, etc. (patient characteristics, not demographics) should be presented, with an indication of the general state of health and type of operation being undertaken. Animal data on sex, strain and weight should be included. Although it is usually possible to make such a statement in a short paragraph, more complex information may be preferable as a table. However, tables and figures are expensive to produce and should not be used unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

CLINICAL TRIALS

In accordance with the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors (see here), all clinical trials in British Journal of Anaesthesia must be registered in a public trials registry at or before the onset of participant enrollment. This requirement applies to all clinical trials that begin enrollment after 1 January 2009. For trials that began enrollment before 1 January 2009, registration is strongly recommended and if the trial reported was not registered, please comment on this matter in the covering letter.

Research is considered to be a clinical trial if it involves prospective assignment of human subjects to an intervention or comparison group to study the relation between a health-related intervention and a health outcome. Further details of which clinical trials are covered by this policy are in the updated ICMJE guidelines available here.

The registry must be accessible to the public at no charge, searchable, open to all prospective registrants, and managed by a not-for-profit organization. The registry must include the following information: a unique identifying number, a statement of the intervention(s), study hypothesis, definition of primary and secondary outcome measurements, eligibility criteria, target number of subjects, funding source, contact information for the principal investigator, and key dates (registration date, start date, and completion date). The following registries are recommended by ICMJE: Clinical Trials, ISRCTN Register, UMIN Clinical Trials Registry, Australia New Zealand Clinical Trials Registry, Nederlands Trial Register.

In accordance with the ICMJE's recommendation, British Journal of Anaesthesia will also accept registration of clinical trials in any of the primary registers that participate in the World Health Organization's International Clinical Trial Registry Platform (see here). Primary

registers are WHO selected registers managed by not-for-profit entities that will accept registrations for any interventional trials, delete duplicate entries from their own register, and provide data directly to the WHO. Please note that registration in any WHO partner register is insufficient.

Authors are requested to provide the exact URL and unique identification number for the trial registration at the time of submission. This information will be published in the article and we ask that you include the URL and identification number on the title page of your manuscript.

Clinical trial reports should also comply with the Consolidated Standards of Reporting Trials (CONSORT) and include a flow diagram presenting the enrollment, intervention allocation, follow-up, and data analysis with number of subjects for each (see here). Please also refer specifically to the CONSORT Checklist of items to include when reporting a randomized clinical trial.

Results posted in the same clinical trials registry in which the primary registration resides will not be considered prior publication if they are presented in the form of a brief abstract (500 words or less) or a table.

RESEARCH USING ANIMALS

Institutional approval

Studies that involve the use of animals must clearly indicate that Institutional approval was obtained and state the UK Home Office Licence number or local equivalent that the studies were performed under. It is recognized that animal welfare legislation can vary between countries and so the BJA uses the UK standards as a baseline and reserves the right to reject manuscripts judged not to meet these standards, even when local approval has been granted.

Anaesthesia

The methods of anaesthesia and analgesia for research studies involving animals should be the best available to ensure the welfare of the animals involved. Reducing the potential for pain and distress is a significant refinement and provision of safe and effective anaesthesia that does not interfere with specific research objectives also reduces the numbers of animals used. Authors must also state how they assessed and monitored the adequacy of anaesthesia. Some anaesthetics may have interactions that are important to certain areas of research. For example medetomidine and xylazine both cause hyperglycaemia, osmotic diuresis, and effects on the cardiovascular system. When used in conjunction with ketamine, these agents both produce surgical anaesthesia in rodents, suitable for a range of different operative procedures. However the side-effects may make them unsuitable for certain types of research. The safe dose of intra-peritoneal pentobarbital in rats has a narrow range and unpredictable duration; indeed a larger dose is often used for killing an animal at the end of a procedure. Whichever agent is used, an appropriate plane of anaesthesia for the intervention must be assessed and achieved. This is particularly important when neuromuscular blocking agents are used.

Information on potentially suitable anaesthetic regimens can be obtained from a variety of sources, including the veterinary advisor at your research institution, specialist laboratory animal anaesthesia and general veterinary anaesthesia textbooks. Obtaining information on potential interactions with research procedures is less easy to obtain and frequently requires a careful literature search. The agents available and the techniques for their administration are evolving so selecting the method used in other scientific publications will not guarantee the most appropriate method. The choice of anaesthetic and route of administration should:

- Provide the required depth and duration of anaesthesia for the procedure
- Be simple to administer, without distress to the animal
- Should be free from undesirable side effects and allow uncomplicated recovery
- Should cause the minimum of interference with the purpose of the research procedure

Analgesia

When animals are used in biomedical research, every effort should be made to minimise any pain or distress. Not only is this important for ethical reasons, but also because pain is a source of stress that can cause undesirable effects on the outcome of research projects. Considerable progress has been made over the last 10-15 years in preventing or alleviating pain. In particular, there is now considerable opportunity to minimise or eliminate pain following surgical procedures. A wide range of analgesics are available, and it is a simple process to administer one of these agents to prevent or alleviate postoperative pain. It is also important to:

- Administer an appropriate analgesic that provides the required intensity of pain relief
- Administer the analgesic at an appropriate dose
- Continue its administration at appropriate time intervals
- Stop administering the analgesic at an appropriate time after surgery

Provision of effective pain relief requires that all of these points are addressed, but this can only be done by assessing the degree of pain experienced by the animal involved. Animal pain assessment is difficult and time-consuming to implement effectively, so that it is tempting to simply give all animals a "standard dose" of analgesic. In man, the use of such fixed dose regimens has been identified as one of the factors contributing to inadequate pain management, so this approach should be avoided when dealing with laboratory animals.

In humans, analgesic dose rates are based on clinical trials, using well-established methods of assessing pain. In animals, we are unable to assess the severity of many types of pain accurately. Often, all that is possible is to use dose rates that have been established to be safe and effective in some of the tests used in rodents during early drug development. Provided these limitations are appreciated, there are some strategies for pain management which make best use of our existing knowledge:

- If methods of pain assessment have been developed for the species used, then these should be adapted to the requirements of the particular research procedure being undertaken
- If methods of pain assessment are not available, consider devoting resources to developing some form of scoring system

• If pain scoring is not possible, determine the analgesic protocol based on clinical experience with other surgical procedures in that species
• If possible, use dose rates that have been established using studies that have employed pain scoring systems
• Use pre-emptive analgesia and consider using several analgesic agents
• Attempt to evaluate the efficacy of the analgesic regimen selected using clinical assessment (your veterinary advisor will be able to help you to recognise pain in laboratory animals)
• Prepare a rescue analgesia protocol and an immediate euthanasia protocol for animals which appear to be in severe pain

The use of animal models of pain to investigate analgesia techniques is a particular minefield for journals in the field of anaesthesia. Such studies must be conducted with extremely careful regard to animal welfare. Rarely will this journal publish studies where an analgesic agent has been compared to a placebo in an animal model of severe pain.
The book 'Laboratory animal anaesthesia' by Professor Paul Flecknell (3rd Edition, 2009, Academic Press) provides a very helpful introduction for research workers for safe, effective and appropriate anaesthesia and analgesia in animals used in research studies.

Euthanasia

Euthanasia is defined as a pain-free or stress-free death and animals used for research are usually euthanized at the end of a study for the purpose of sample collection or post-mortem examination. Animals may also be killed because they are experiencing severe pain or distress. The method of killing the animal after the experiment is completed should be chosen carefully and must be detailed in manuscripts. The method used should be appropriate to the species and the method used should not confound any objective of the research - veterinary advice should be sought. The conduct of euthanasia for those working with laboratory animals in the UK is quite straightforward. Either the Code of Practice for the Humane Killing of Animals under Schedule 1 to the Animals (Scientific Procedures) Act 1986 is followed or a project and personal licence authorisation is obtained to use a technique not covered by this Code. An updated code of practice for schedule 1 killing has been published by the Animal Procedures Committee and is available online at:
http://apc.homeoffice.gov.uk/reference/schedule-1-report.pdf

The use of carbon dioxide for killing is a subject of much debate and is not suitable for rabbits. For rodents, the use of carbon dioxide is still permitted but other methods are preferable. When carbon dioxide is used, do not pre-fill the cage or chamber with carbon dioxide and use slow filling rates to minimise discomfort. The flow rate can be increased when the animal is unconscious.

ARRIVE guidelines

The contribution of animal research in enabling better health for man and animals is incontrovertible and the BJA is committed to the publication of research studies which use animal models, but demands the same rigorous attention to detail as in clinical trials. Failure

to describe research methods and to report results appropriately has scientific and ethical implications for the entire research process and the reputation of those involved in it.

Experiments involving animals should be appropriately designed, correctly analysed and then transparently reported, to both increase the validity of the results, and maximise the scientific gain. A minimum amount of relevant information must be included in manuscripts published in this journal to ensure that the methods and results of a study can be reviewed, analysed and repeated. The BJA will therefore refer to the ARRIVE (Animals in Research: Reporting In Vivo Experiments) guidelines as the basis for the process of reviewing manuscripts of research involving animals.

These guidelines were generated by The National Centre for the Replacement, Refinement and Reduction of Animals in Research, which is an independent scientific organisation, established by the UK Government, in consultation with scientists, statisticians, journal editors and research funders.

ANAESTHESIA

Descriptions of methods of anaesthesia are often unnecessarily cumbersome. The following model is presented as an example of economy of words: The patients did not receive premedication. Anaesthesia was induced with propofol 2 mg kg -1 and fentanyl 1.5 µg kg -1 . Vecuronium 0.1 mg kg -1 was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with sevoflurane 1.5-2.0% and nitrous oxide 60% in oxygen, with positive pressure ventilation in a circle system. A similar description should be used for animal anaesthesia.

STATISTICAL ANALYSIS

Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple P value. A power analysis should be performed before starting the study to determine the number of subjects which need to be studied in each group to detect a given change. Please note that a power analysis based on the primary end-point will not necessarily be applicable to any secondary measures.

It is recommended that authors seek appropriate statistical advice before starting their study, to ensure that the structure and planned recruitment is adequate to answer the question set.

RESULTS

Guidance for this section includes;

- Must be factual
- Relate to aims
- Logical order
- State significances
- Negative findings

From January 2009, all randomized control trials (RCTs) must adhere to the Consort guidelines and present a flow diagram which details the conduct of the study (http://www.consort-statement.org/)

Description of experimental results should be concise. They should be presented in a factual manner and related to the aim of the study. It is often useful to present the results in the order described in the Methods section. Data should not be repeated unnecessarily in text, tables and figures (see below), and unwarranted numbers of digits should be avoided (Example: the mean dose of propofol was 2.1 mg kg -1 rather than 2.0897 mg kg -1). It may not be necessary to provide all the data from a complex study: only those values which are essential to the communication should be given. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so numerous that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. Where appropriate, for example in a pharmacokinetic study, more extensive sets of data can be included as an appendix with the on-line version of the article. If authors wish to make use of this facility, they should state this in the submission letter and upload the data as a separate file. The editor has the right to request the original data collected. In the results section there should be no attempt at a discussion of the findings.
TABLES AND FIGURES

Figures and Tables are often useful to present either complex or extensive data in a more easily understandable form. However, authors are cautioned against unnecessary use of tables and figures. A useful approach is to prepare the raw data in the form of tables and then decide which data are to be presented in the article. The author should then decide whether the essential data be presented succinctly in the text. If not, the essential tables/ figures should be prepared. To illustrate this with examples: a study outcome which compares two measurements in two groups can easily be presented as text, a comparison of arterial pressure and heart rate changes at five timepoints in two groups would be appropriate as a table and the same measurements in comparing three groups may be better as a figure.

Tables and figures are important communications and should be accompanied by a legend which makes it self-explanatory. However, the legend must not contain experimental details, which should be given in the methods section.

The use of a figure should be considered only where a figure will present the data more clearly than is possible in a table or when an important trend or comparison has to be made for which a graphic presentation is clearly superior to a table or text.

The authors should decide which form they wish to present data in. Please note the limitation given above on the number of figures/tables permissible for each article type. Duplication of data by including it as a table and as a figure is unnecessary and wasteful.

Authors are advised to note the limitation on the number of figures/tables given above (4-6 tables or figures, in total) for clinical and laboratory investigations and 1 figure or table for a case report or editorial. The use of multiple small figures submitted as one figure (for example Figure 1 a-f) is discouraged as when reduced to printed size these may not be clear. Authors are strongly advised to be selective in their use of figures and tables.

For further guidance on the format of tables and figures, see below. It is recommended that the author refers to previous issues of the journal regarding appropriate style.

DISCUSSION

This is an important part of the manuscript but it should not be too long, perhaps one third of the total length of the paper. This requires discipline by the author for two reasons: first, they may feel that the task is nearly completed and that they are subject to fewer constraints; second, many authors seem to wish to read into their data more than is actually there.
It is suggested that the discussion should normally follow the pattern below:

- State main findings
- How do they fit in with previous studies
- Why are they different / same
- What it adds to knowledge of subject
- Weaknesses in study
- Future studies
- Conclusions

State main findings

This does not mean a repetition of all the results with their statistics. It should provide a concise overview of the study. For example, ' Drug X produced a greater haemodynamic change on induction of anaesthesia than occurred with drug Y, resulting in a greater fall in arterial pressure and a higher incidence of tachycardia '.

How do they fit in with previous studies

This section should relate directly to the statements made in the Introduction and qualify you finding in relation to the previous studies of the subject. For example, mention any important uncertainties in the methods of measurement. In laboratory studies, try to relate the concentrations used to those encountered clinically.

Why are they different / same

Deductions which may explain important differences between the data of the present study, and the data of previous studies. The author should avoid excessive speculation in this section. It is quite reasonable to suggest possible explanations for your findings and any differences from previous studies but the 'missing parts' of such reasoning must be acknowledged.

What it adds to knowledge of subject

This can summarise the previous sections by pulling together the implications of your main findings, studies by other workers and their combined contribution to our knowledge of the subject. This should not be just another repetition of the results and preceding discussion but more of an expanded conclusion.

Weaknesses in study
It is appropriate to briefly acknowledge any limitations of your study at this point. Examples here could include the patient population, limitations of analytical tests, patients lost to follow-up. Authors are advised to be honest but succinct in this section.

Future studies
A logical follow on to the two previous sections is to identify future studies that would address some of the potential explanations and limitations discussed earlier. This should again be concise. An extensive list of future studies undermines you own study: i.e. has it answered anything if there are still so many questions?

Conclusions
Conclusions from the present study. The original contribution to knowledge from the present study is stated. A common fault here is to overstate the findings from a study. For example, if you have studied the effect of a new drug in an animal model you cannot draw any conclusions at all about its effect in humans and likewise if you studied ASA 1 and 2 patients you cannot comment on its use in critically ill patients.
It may be appropriate to give the implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.
Authors should remember at all times, but especially in writing the discussion, that they will spoil their manuscript by excessive length. A discussion of more than three pages is often too long.
DECLARATION OF INTERESTS

It is essential to acknowledge all sources of financial assistance, and any potential material benefit expected from publication of the work. Also, please describe the role of the study sponsor, if any, in study design; collection, analysis and interpretation of data; writing the report; and the decision to submit the report for publication.

Each manuscript must contain a declaration of interests from ALL authors. This should include all possible interests in the past five years. This is obviously most common in studies involving new equipment or drugs, but other areas such as advisory bodies are also relevant.

For example: 'Dr A has received an honorarium from Company X. Dr B has received a travel grant from Company Y. Prof C is a member of the national advisory committee on Z.'

You are required to declare all authors' interests at the time of submitting your manuscript by completing and uploading a conflict of interest form. Please upload it as a separate file labelled “conflict of interest form” along with your manuscript. Failure to do so will lead to delays in the processing of the manuscript. Please make sure that information from all authors

has been included before uploading, even if there are no interests to be declared. A form must be submitted even if there is no conflict of interest. The corresponding author of an article acts as guarantor and must ensure that this criterion is fulfilled and a full conflicts of interest statement is supplied to the Journal.

A conflict of interest statement must also be included in the manuscript after any "Acknowledgements" and "Funding" sections and should summarize all aspects of any conflicts of interest included on the form. If there is no conflict of interest, authors must include ‘Declaration of Interest: none declared'.

FUNDING

Details of all funding sources for the work in question should be given in a separate section entitled 'Funding'. This should appear before the 'Acknowledgements' section.

The following rules should be followed:

The sentence should begin: ‘This work was supported by …’
The full official funding agency name should be given (one of the 27 subinstitutions), i.e. ‘National Institute for Academic Anaesthesia’, not ‘NIAA’ or 'NCI at NIH’ (full RIN-approved list of UK funding agencies)
Grant numbers should be complete and accurate and provided in brackets as follows: ‘[grant number ABX CDXXXXXX]’
Multiple grant numbers should be separated by a comma as follows: ‘[grant numbers ABX CDXXXXXX, EFX GHXXXXXX]’
Agencies should be separated by a semi-colon (plus ‘and’ before the last funding agency)
Where individuals need to be specified for certain sources of funding the following text should be added after the relevant agency or grant number 'to [author initials]'.
An example is given here: ' This study was funded by a small project grant from The Royal College of Anaesthetists (07/123) (AB). Equipment was provided by a project grant from British Journal of Anaesthesia/RCoA (06/321) (CD) .'

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All manuscripts submitted to BJA must inform the readers of individual contribution which each author made to the research and/or manuscript.

Please give initials of the names of each of the authors (i.e. R.D., I.K.M.) , and against their initials list the contributions which they individually made to the work (i.e. R.D. : Study design and data analysis; I.K.M.: Patient recruitment, data collection and writing up of the first draft of the paper).

Each author must take responsibility for at least one component of the work, should be able to identify who is responsible for each other component, and should ideally be confident in their co-authors' ability and integrity.

The British Journal of Anaesthesia follows recommendations of International Committee of Medical Journal Editors (ICMJE). To comply with ICMJE recommendations, all the authors must meet all of the following four conditions:

substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data;
drafting the article or revising it critically for important intellectual content;
final approval of the version to be published; and
agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

For large, multicentre studies, the group of investigators should identify individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship.

If the author list includes a group name all members of the group must meet the full criteria and requirements for authorship as described above. If all members of a group do not meet all authorship criteria, a group must designate one or more individuals as authors or members of a writing group who meet full authorship criteria and requirements. Other group members who are not authors may be listed as Collaborators (sometimes called non-author contributors). These will be listed on PubMed as collaborators rather than authors. In order to be indexed as collaborators, the names of the consortium or working group members should be listed in an Appendix in the main text document, before the Reference list. The consortium or working group should also be included in the main author list. PubMed will list the names of individual group members who are authors or collaborators. There should be a note associated with the author list clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators. Collaborator names are searchable on PubMed in the same way as authors. PubMed rules for this can be found here.
ACKNOWLEDGEMENTS

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REFERENCES

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in Index Medicus and Index Veterinarius journals.

Please avoid inappropriate and/or excessive self-citations. Appropriate self-citations are welcome.
References must be numbered consecutively in the order in which they are first mentioned in the text.
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Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Personal communications should be cited in the text as (Brown AB, personal communication, year). Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. This should be provided in writing with the first submission of the manuscript.
Papers which have been submitted and accepted for publication should be included in the list, with the phrase 'in press' replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction. Abstracts should also be sent with the original submission.
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Myles PS, Chan MTV, Leslie K, Peyton P, Paesch M, Forbes A. Effect of nitrous oxide on plasma homocysteine and folate in patients undergoing major surgery. Br J Anaesth 2008; 100 : 780-6
Chapter in a book. The reference for an article forming part of a book should take the form:

Wildsmith JAW. Local anaesthetic agents. In: Aitkenhead AR, Smith G, Rowbotham DJ, eds. Textbook of Anaesthesia. Edinburgh: Churchill Livingstone Elsevier, 2007; 52-63

Electronic source (web site/web page) :

Department of Health. Monthly Creutzfeldt-Jakob disease statistics 2002/0341 2002. Available from http://www.doh.gov.uk/cjd/stats/aug02.htm (accessed 30 March 2010)

Online journal article :

Lander JA, Weltman BJ, So SS. EMLA and amethocaine for reduction of children's pain associated with needle insertion. Cochrane Database Syst Rev 2006; 3 : CD004236

Proceedings :

O'Rourke K. Mixed means and medians: a unified approach to deal with disparate outcome summaries. Proceedings of the Symposium on Systematic Reviews: Pushing the Boundaries . Oxford: 2002; 49

Report :

Royal College of Anaesthetists and Royal College of Radiologists. Sedation and Anaesthesia in Radiology . Report of a joint working party, London, 1992

Advance access article :

Qiao D, Chen W, Stratagoules E, Martinez J. Bile acid-induced activation of activator protein-1 requires both extracellular signal-regulated kinase and protein kinase C signaling. J Biol Chem Advance Access published on May 19, 2000, doi:10.1074/jbc.M908890199
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PREPARATION OF TABLES

Tables must be supplied in an editable format (e.g. in Word or Excel) not as images, as they need to be edited to journal style. Failure to supply tables in editable format will delay publication.

All tables should be on separate sheets and accompanied by legends. Legends should be informative but brief and not contain information which is more appropriate to Methods. It is preferable to present the data in table format, in either Word or Excel, but not as images that cannot be accessed for editing. The tables should be numbered consecutively using Arabic numerals. Units in which results are expressed should be given in parentheses at the

top of each column and not repeated in each line of the table. Ditto signs are not used. Avoid overcrowding the tables and the excessive use of words. The format of tables should be in keeping with that normally used by the journal; in particular, vertical lines should not be drawn. Please be certain that the data given in tables are correct, as changes at the proof stage are particularly expensive.

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As the journal is now printed in full colour, there is no charge to authors for colour reproduction. It can help avoid delays in publication if line drawings are supplied using the journal's agreed colour palette:

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Accuracy in the preparation of figures is essential as is the appropriate use of symbols and abbreviations (see below).

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The British Journal of Anaesthesia uses the SI system of units with a few notable exceptions (pH and intravascular and ventilatory pressure measurements, which should be given in units of calibration, e.g. mm Hg, cm H 2 O). Blood-gas tensions and the partial pressures in the gas phase should be given in the appropriate SI unit (kPa for kilopascal). It is not intended to give a detailed account of the SI system, the notation of units, symbols and abbreviations in this document. Readers are referred to Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors , 4th Edn. Baron DN, ed. (1988), published by and available from the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE.

Particular problems have arisen in relation to the notation of units which was introduced at the same time as the change to the SI system. Avoid the use of the solidus (/) in favour of various units of the expression set on one line. In the case of expressions 'below the line' superscript -1, -2, etc. as appropriate is given. Thus for drug dosage use mg kg -1 not mg/kg.

SPELLING AND GRAMMAR

Standard Oxford UK English should be used. Examples: anaesthesia, haemorrhage, organization.

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Each issue of the journal will contain correspondence (Letters to the Editor). We aim to publish correspondence arising from papers in a recent issue with the minimum of delay, and for this reason such correspondence will be given priority. The Editor may change, delete or modify in any way all items of correspondence.

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Stewart, Richard A, 2015 DAS Guidelines: the end for pre-paralysis mask ventilation check? Comment published 13 December 2015, accessed 20 March 2017 on C. Frerk, V. S. Mitchell, A. F. McNarry, C. Mendonca, R. Bhagrath, A. Patel, E. P. O'Sullivan, N. M. Woodall, I. Ahmad, Difficult Airway Society intubation guidelines working group; Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth 2015; 115 (6): 827-848. doi: 10.1093/bja/aev371

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