

ORIGINAL ARTICLE

A prehospital randomised controlled trial in South Africa: Challenges and lessons learnt

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ARTICLE INFO

Keywords:

ST-elevation myocardial infarction
South Africa
Telemedicine
Randomised controlled trials
Research methods

ABSTRACT

The incidence of cardiovascular disease and STEMI is on the rise in sub-Saharan Africa. Timely treatment is essential to reduce mortality. Internationally, prehospital 12 lead ECG telemetry has been proposed to reduce time to reperfusion. Its value in South Africa has not been established. The aim of this study was to determine the effect of prehospital 12 lead ECG telemetry on the PCI-times of STEMI patients in South Africa. A multicentre randomised controlled trial was attempted among adult patients with prehospital 12 lead ECG evidence of STEMI. Due to poor enrolment and small sample sizes, meaningful analyses could not be made. The challenges and lessons learnt from this attempt at Africa's first prehospital RCT are discussed. Challenges associated with conducting this RCT related to the healthcare landscape, resources, training of paramedics, rollout and randomisation, technology, consent and research culture. High quality evidence to guide prehospital emergency care practice is lacking both in Africa and the rest of the world. This is likely due to the difficulties with performing prehospital clinical trials. Every trial will be unique to the test intervention and setting of each study, but by considering some of the challenges and lessons learnt in the attempt at this trial, future studies might experience less difficulty. This may lead to a stronger evidence-base for prehospital emergency care.

African relevance

- Cardiovascular diseases and STEMI are on the increase in Africa and other LMICs.
- Prehospital 12 lead ECG telemetry has not been tested in Africa before, and carries significant cost.
- An African evidence-base for this prehospital practice is lacking, or of a poor standard.
- Some specific challenges and lessons are outlined for future attempts at prehospital RCTs in Africa.

Introduction

Globally the incidence of cardiovascular disease (CVD) is on the rise. This is appreciable both in developed and developing economies [1,2]. Ischaemic heart disease was responsible for 13.3% of all deaths worldwide in 2010 and the years of life lost to ischaemic heart disease increased by 28% from 1990 to 2010 [2]. Within Africa, CVD is

considered to be the second most common cause of death, after infectious disease; and accounts for 10% of all deaths [3]. These estimates are largely based on limited data [4]. However, despite this paucity of data, an upward trend in the incidence of cardiovascular disease is seen – a doubling of the incidence was expected between 2009 and 2020 [3]. Within South Africa, CVD is the culprit in death 17.8% of the time, and is currently on an upward trend too [5].

ST-segment elevation myocardial infarction (STEMI), is a life-threatening consequence of the disease progression of CVD. Among 19 LMICs, approximately 46% of patients with acute coronary syndromes present with STEMI - slightly higher than the 41% STEMI incidence reported in South Africa [6]. Timely reperfusion of these patients is essential, as each 30 min delay in reperfusion may increase one-year mortality by 7.5% [7]. In order to minimise delays in reperfusion, the European Society of Cardiology recommends that a 12 lead electrocardiogram (ECG) is performed to confirm STEMI diagnosis and transmitted to a PCI capable hospital within 10 min of the first contact with a healthcare provider (first medical contact, FMC) in the

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Received 28 August 2018; Received in revised form 1 December 2018; Accepted 3 February 2019

Available online 06 March 2019

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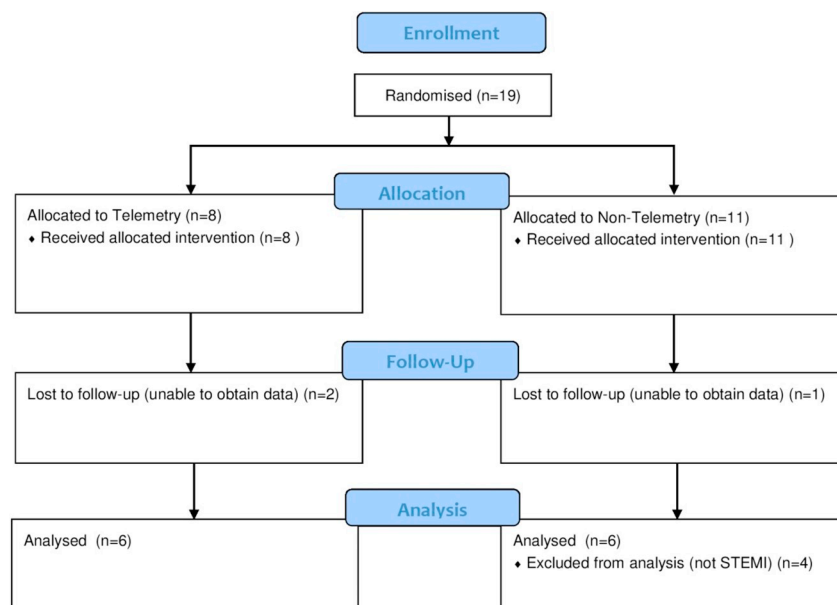


Fig. 1. Patient flow diagram.

prehospital setting [8]. Twelve lead ECG telemetry has been associated with a mean decrease in reperfusion times of 41 min [9]. These findings have been corroborated in Japan [10], the United States [11] and Denmark [12].

The aim of the study was to determine the effect that prehospital twelve lead ECG telemetry had on the PCI-times of patients diagnosed with STEMI in the South African setting; by conducting a multicentre randomised controlled trial (RCT).

RCTs have long been held as the gold standard for clinical research and were first introduced in 1948 for the evaluation of the effect of streptomycin in the treatment against tuberculosis [13–15]. An RCT is a clinical trial that involves the random allocation of two cohorts of patients to receive either an intervention (experimental group) or another alternative (control group) [16]. The two groups are followed to determine whether there are any differences observed in a predefined outcome [16]. Unfortunately prehospital RCTs are uncommon and the majority of studies are more observational in nature [17,18]. This is largely due to the complexity of conducting RCTs including the associated time and costs [18].

Performing an RCT in the prehospital setting in South Africa proved to be a challenge. The trial ran over 28 months and only enrolled 19 patients. In the current paper we summarise some of the results of the trial, challenges and lessons learnt from the process of performing, to our knowledge, Africa's first prehospital RCT.

Methods

A multicentre, parallel randomised controlled trial was undertaken in the Gauteng and Western Cape provinces of South Africa. The study was conducted in 3 private EMS bases and 6 urban hospitals with 24-hour PCI capability between July 2015 and October 2017. The trial was registered with clinicaltrials.gov (NCT02441582) and the South African National Clinical Trials Registry (DOH-27-0515-4657). Ethical approval was obtained from the Human Research Ethics Committee of Stellenbosch University (M14/07/027).

Adult patients (<18 years) with chest pain or dyspnoea presumed to be of cardiac origin with prehospital 12 lead ECG evidence of STEMI were enrolled. STEMI (and eligibility for enrolment) was diagnosed by paramedics using the Third Universal AMI definition [19]. Patients were excluded according to predetermined exclusion criteria. If the closest PCI-capable facility did not participate in the study, the patient

was not enrolled. The a priori sample size was determined to be 100 at a 1:1 allocation ratio to detect a 15-minute mean reduction in the reperfusion time for the telemetry group (power = 95%, alpha = 0.05).

Rapid response vehicles were dispatched to all cases of chest pain. On arrival at the patient, a twelve lead ECG was performed to confirm the diagnosis of STEMI by the attending paramedics. After confirmation of STEMI, informed consent was obtained and patients were randomly allocated by a priori simple computer randomisation (SPSS version 22, IBM Corp., New York, United States) to a telemetry (Tel) or non-telemetry (N-Tel) group in a 1:1 ratio. Randomisation was done by opening a sequentially numbered, opaque envelope. Patients were assigned to each group by the attending ALS paramedic.

All patients were given standard prehospital STEMI care by paramedics according to the current accepted prehospital emergency care protocols in South Africa [20]. For the Tel-group, the 12 lead ECG was sent through a central server to a fax machine located in the closest participating PCI-capable facility, located in the Emergency Centre. From here, the ECG was rerouted to an email address and forwarded to the on-call cardiologist for that specific hospital via email. Receipt of the ECG was confirmed telephonically. The patient was then transported to this hospital where standard procedures were left uncontrolled. For patients in the N-Tel group, the ECG was not sent, and the patient was still transported to the closest participating hospital. Patients were followed until PCI, or for 12 h, whichever came first.

Descriptive data are presented as median and interquartile range to account for outliers. Due to small sample sizes obtained, statistical analysis would not be appropriate and was therefore not performed.

Results

Nineteen (Tel, $n = 8$; N-Tel $n = 11$) STEMI patients were enrolled in 28 months. Fig. 1 shows the allocation and follow-up of participants. Our final sample size for analysis was 12 (Tel, $n = 6$; N-Tel, $n = 6$). The trial was stopped as no more patients were being enrolled, and further conduct of the trial seemed futile. The PCI timelines are summarised in Table 1.

Discussion

The aim of this study was to determine the effect of prehospital 12 lead ECG telemetry on the PCI-times of STEMI patients in South Africa.

Table 1
Treatment timelines per group.

	Tel-Group	N-Tel-Group	Difference
Onset-to-FMC, M(IQR)	52.5 (9.1) min	52 (776.2) min	0.5 min
Scene time, M(IQR)	30.5 (5.5) min	41 (10.8) min	– 10.5 min
Door-to-PCI, M(IQR)	80 (492.8) min	106.5 (648.3) min	– 26.5 min
Onset-to-PCI, M(IQR)	476 (553.5) min	542 (866.5) min	– 66 min

FMC=first medical contact, M = median, IQR = interquartile range, PCI=percutaneous coronary intervention.

Performing this trial proved to be a challenge with low enrolment rates leading to a failure to achieve adequate sample sizes. For this reason, the true value of the study lies in the lessons learnt, rather than the results obtained. Some specific challenges related to the unique South African healthcare landscape, resources, training of paramedics, rollout and randomisation procedures, technology, consent and the South African prehospital research culture. Each of these aspects is discussed in turn.

The South African (and some African) healthcare landscape has two distinct sectors, private and state. The private sector is well-resourced and tends to provide healthcare services to South Africans who are concentrated in the urban environment, who are of a higher socio-economic status and are employed [21]. Most often, these patients have medical insurance and account for but 18% of the population [22]. In contrast, the state healthcare system is characterised by a general lack of human resources, financial constraints and dated infrastructure, yet serves the vast majority of South Africans [21].

The lack of state healthcare resources remains true for patients requiring PCI [23]. There is a shortage of PCI-capable facilities in South Africa nationally (there is one facility for every 887,096 people), and only 23% of the facilities are contained within the state healthcare system [23] but serves roughly 82% of the South African population.

In planning this study, primary PCI within the state healthcare sector was going to be unrealistic, and therefore the decision to seat the RCT in the private sector. The private EMS may however, not refuse response to patients based on their insurance status, but because they cannot be taken to private healthcare facilities for PCI, these patients were not eligible to be enrolled into the RCT. This greatly reduced the number of eligible patients to enrol. Consequently, the recruitment and sample size suffered. It is recommended that future studies consider the unique challenge of insurance status of the healthcare landscape and provide opportunity for the uninsured majority to be also enrolled in these studies. This will also allow for greater external validity of the results, and ethically more patients could then potentially benefit from the intervention. This recommendation remains true for other LMICs with dual sectorised healthcare.

To cut costs, resources that were already available within the system were utilised. By doing this, the validity of the study increases as it becomes more representative of the current situation in which clinical care is taking place. This also means that expensive resources will not have to be purchased. Costs were mainly related to the printing of study documentation and enrolment packs and did not include other healthcare costs associated with the care of patients enrolled in the study. Cost-saving measures should be offset with the appropriateness of the resources available to achieve the aim of a trial in future.

Volunteers which acted as research assistants to ensure follow-up and data gathering, were utilised. This was one of the principal weaknesses of our study. By employing research assistants, there can be accountability and a vested interest in ensuring follow-up. It is suggested that budgeting for salaries for these assistants be considered as a bare minimum expenditure. This allows for a dedicated resource that can track and trace patients and continuously communicate to paramedics expected to enrol patients. Constant communication, through dedicated channels has been known to improve protocol compliance and recruitment [24]. One way of doing this with limited funding may

be to second operational paramedics to coordinate the study [25].

Novel means of doing low-cost RCTs do exist [26], and can be facilitated by using existing data (such as population surveys or mortality registers) or embedding the study into existing evaluation programmes. It is essential to plan research projects within other programmes a priori, as many of the administrative and staff costs can be covered within the programme budgets [26]. Within the African context, such resource-lean approaches should be developed and employed towards the generation of good quality evidence [24].

Advanced Life Support (ALS) paramedics at the EMS bases were trained face-to-face, either by the principal investigator or one of the research assistants before the start of the study. Training lasted approximately two hours and involved information on the study design, the enrolment procedure (including inclusion and exclusion criteria) and follow-up of patients and obtaining informed consent. Further clinical training was given on twelve lead ECG analysis and STEMI diagnosis.

Due to shift work, geographic dispersion of bases, and the dynamic nature of EMS, there was great difficulty with getting all paramedics (who acted as recruiters) together simultaneously, and this meant that numerous training sessions needed to occur. Training and retraining were further compounded by poor staff retention and great turnover of ALS paramedics. Many studies have outlined the concerns with paramedic emigration from South Africa, and presented some suggestions on how to improve staff retention [27–29]. Regardless of the reasons or setting, poor retention complicates the continuity of patient enrolment and requires additional resources for training on the study procedures as new staff join.

Face-to-face training regarding study procedures can be replaced by an online training module instead. Such an approach has been used previously within the setting to improve traumatic brain injury guideline adherence [30]. This allows for self-paced learning that can span across shift work and geographic dispersion and is dynamic enough to allow for training of new staff during organisational orientation.

Rollout of the project started at all EMS bases simultaneously. However, in some of these areas a participating PCI hospital had not yet been identified or consented to participating in the study. This meant that initial enthusiasm from paramedics faded early, as paramedics were unable to enrol patients as a participating hospital was not available. Further frustration was encountered due to difficulties with the telemetry technology – discussed in a later section.

In retrospect, it is suggested that future trials be started on a much smaller scale and optimised to allow for testing of study procedures and to elicit immediate feedback from a small group of paramedics, addressing any issues or misunderstandings early on [24]. Further to this, focusing on a smaller group may allow for more intensive support to those enrolling and could facilitate in building a better research culture. One method of starting the study on a smaller scale is to employ a stepped wedge randomisation design [31].

Prospective computer randomisation, with use of sequentially numbered, opaque envelopes was employed. Often, those obtaining consent or enrolling patients were confused as to the randomisation procedures and would phone the principal investigator prior to enrolling patients to confirm cohort allocation. The study procedures were then reiterated.

Such uncertainty threatens breach of protocol and could impact on the quality of conclusions. A stepped wedge randomised trial is a relatively novel research trial design that is starting to gain popularity [31]. Within this design, the intervention being studied is rolled-out sequentially to participants (or base clusters in the case of this RCT) over several time periods. After the data collection period, all of the base clusters would have received the intervention however, the order with which the intervention is received is determined at random [31,32]. A stepped wedge design is particularly attractive in instances where the simultaneous delivery of an intervention is impractical or impossible due to political, logistic or financial reasons [32]. Future

studies within the African prehospital context should consider employing this design instead as it provides a pragmatic, scalable means of systematic study.

We used resources already contained within the setting. The specific prehospital 12 lead monitor that was in circulation required a link to a mobile phone via Bluetooth® version 2.1 (adopted in 2007). Hereafter, the 12 lead ECG obtained was sent to a central server from where it would be redirected to a pre-loaded fax number of the particular PCI-hospital nearby. Moments later, a fax would be delivered to the hospital.

Unfortunately, at the time of the study most mobile phones using this out-dated Bluetooth® technology was no longer in circulation, and thus sourcing these devices was incredibly difficult. Once sourced, further difficulties would be encountered as sim cards would run out of mobile airtime or would not have regular battery charging – leaving mobile phones with flat batteries when needed to enrol patients. Charging facilities, battery life and the cost of mobile data should be taken into consideration in any African trial with a reliance on mobile technology, albeit for enrolment, allocation or data capture.

It was a surprise that most hospitals did not have fax capabilities any longer. In addition, computer or fax-to-email services were only accessible to managers who were unavailable after hours. For these reasons, this intervention may not be the most practical solution for the low-resource setting.

For future studies, it is essential that solutions be thoroughly considered for practical application within the African context. Failing this, studies might be unsuccessful for the simple reason that the solution is not tailored to the setting in which it is intended to fit.

The telemetry system that was tested utilised relatively old technology and was cumbersome. Further research into a low-resource telemetry solution should be undertaken. One such resource could be Whatsapp Messenger. Whatsapp messenger (Whatsapp Inc. California) is a free instant messaging service that has been used within the setting of STEMI to improve reperfusion times [33]. The use of Whatsapp or similar services may be of particular use to low-resource settings where the acquisition of expensive telemetry systems may not be possible. Whatsapp Messenger was not encrypted at the time of the design and implementation of this study, and concerns regarding patient confidentiality precluded its use [34].

In the context of STEMI, a patient's capacity to provide informed consent for research could be influenced by distress and disorientation due to the patient's medical condition, pain and the effects of analgesia [35]. In the South African prehospital environment, obtaining consent becomes more complex as cultural and language barriers cannot be overcome by the timely involvement of a competent interpreter. This may further impede the ability to treat the patient expeditiously [36]. Clearly, the circumstances to obtain informed consent for prehospital emergency care research are not ideal [37]. In this study, consent to participation was sought prior to randomisation and enrolment. It is anticipated that low enrolment rates could be uneasiness of attending ALS paramedics with obtaining consent from a patient suffering a STEMI [36,37], especially considering that these paramedics would never have been exposed to such procedures before. Deferred or delayed consent has been proposed to overcome some of the challenges associated with obtaining informed consent in emergency care research [37]. Under strict ethical criteria [37,38], delayed consent allows for immediate enrolment of patients into a study, and later consent of patients from a more experienced member of the trials team, in a more controlled environment at a more appropriate time. This is particularly relevant in a trial of this nature that poses negligible risk to participants, and should be considered for future prehospital RCTs.

Studies suggest that research should be prioritised by EMS leaders, and this may promote recruitment and compliance to research protocols. Culture also seems to be related to the previous research experience within the organisation [25]. It is our experience that research is a relatively new endeavour for prehospital care within the South African

context. In a recent African survey, the fourth most common barrier to performing emergency care research was found to be lack of a positive research culture [39]. The leading barrier was a lack of funding, which in itself speaks of a poor research culture [39]. This culture may be improved by incorporating research into everyday operational practice and viewing a research failure in the same light as any other organisational failure [25]. We suggest a local qualitative study among the paramedics involved in this trial to determine what the barriers to enrolment were.

Previous studies have found that the fundamental success of recruitment into a prehospital clinical trial is related to the attitude of the paramedics towards the intervention [40]. Within the organisation where the study was conducted, there has been some resistance to routine twelve lead ECG acquisition and this could further offer explanation to low enrolment.

Conclusion

There is a paucity of high quality research in the prehospital context of Africa. This is likely due to the specific challenges in completing clinical trials within this environment. Every trial will be unique to the intervention being studied and the exact milieu in which the study is being undertaken however, by following some of these recommendations future studies might experience less difficulty. This may lead to improved success and a stronger evidence base for prehospital emergency care in Africa.

Conflicts of interest

Prof Lee Wallis, Dr Willem Stassen and Prof Craig Vincent-Lambert are editors of the African Journal of Emergency Medicine. Profs Wallis and Vincent-Lambert, and Dr Stassen were not involved in the editorial workflow for this manuscript. The African Journal of Emergency Medicine applies a double blinded process for all manuscript peer reviews. The authors declared no further conflict of interest.

Author Contribution

WS conceived the project, collected and analysed and interpreted data, and drafted and approved the final manuscript. LK analysed and interpreted data and approved the final manuscript. LW, CL, MC interpreted data. All authors approved the version to be published and agreed to be accountable for all aspects of the work.

Dissemination of results

The results were communicated with the particular EMS bases and hospitals that participated in the study. Further, publication aims at disseminating findings more broadly.

References

1. Kobusingye OC, Hyder AA, Bishai D, Hicks ER, Mock C, Joshipura M. Emergency medical systems in low- and middle-income countries: recommendations for action. *Bull World Health Organ* 2005;83(8):626–31. [doi:10.S0042-96862005000800017].
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2095–128. [https://doi.org/10.1016/S0140-6736\(12\)61728-0](https://doi.org/10.1016/S0140-6736(12)61728-0).
3. Mbewu A. The burden of cardiovascular disease in Sub-Saharan Africa. *SA Heart* 2009;6(5):4–10.
4. Celermajer DS, Chow CK, Marijon E, Anstey NM, Woo KS. Cardiovascular disease in the developing world: prevalences, patterns, and the potential of early disease detection. *J Am Coll Cardiol* 2012;60(14):1207–16. <https://doi.org/10.1016/j.jacc.2012.03.074>.
5. Statistics South Africa. *Mortality and Causes of Death in South Africa, 2015: Findings From Death Notification* [Stat release P03093]. 11. 2015. p. 1–140.
6. Schamroth C. Management of acute coronary syndrome in South Africa: insights from the ACCESS (Acute Coronary Events - a Multinational Survey of Current Management Strategies) registry: cardiovascular topics. *Cardiovasc J Afr* 2012;23(7):365–70.

- <https://doi.org/10.5830/CVJA-2012-017>.
7. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 2004;109(10):1223–5. <https://doi.org/10.1161/01.CIR.0000121424.76486.20>.
 8. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018;39(2):119–77. <https://doi.org/10.1093/eurheartj/ehx393>.
 9. Brunetti ND, di Pietro G, Aquilino A, et al. Pre-hospital electrocardiogram triage with tele-cardiology support is associated with shorter time-to-balloon and higher rates of timely reperfusion even in rural areas: data from the Bari- Barletta/Andria/Trani public emergency medical service 118 regist. *Eur Heart J Acute Cardiovasc Care* 2014;3(3):204–13. <https://doi.org/10.1177/2048872614527009>.
 10. Kawakami S, Tahara Y, Noguchi T, et al. Time to reperfusion in ST-segment elevation myocardial infarction patients with vs. without pre-hospital mobile telemedicine 12-lead electrocardiogram transmission. *Circ J* 2016;80(7):1624–33. <https://doi.org/10.1253/circj.CJ-15-1322>.
 11. Rao A, Kardouh Y, Darda S, et al. Impact of the prehospital ECG on door-to-balloon time in ST elevation myocardial infarction. *Catheter Cardiovasc Interv* 2010;75(2):174–8. <https://doi.org/10.1002/ccd.22257>.
 12. Sejersten M, Sillesen M, Hansen PR, et al. Effect on treatment delay of prehospital teletransmission of 12-lead electrocardiogram to a cardiologist for immediate triage and direct referral of patients with ST-segment elevation acute myocardial infarction to primary percutaneous coronary intervention. *Am J Cardiol* 2008;101(7):941–6. <https://doi.org/10.1016/j.amjcard.2007.11.038>.
 13. No authors listed. Streptomycin treatment of pulmonary tuberculosis. *Br Med J* 1948;2(4582):769–82.
 14. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Chin J Evid Based Med* 2009;9(1):8–11. <https://doi.org/10.1136/bmj.39489.470347.AD>.
 15. Concato J, Shah N, Horwitz RJ. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000;342(25):1887–92. <https://doi.org/10.1056/NEJM200006223422507>.
 16. Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emerg Med J* 2003;20(2):164–8.
 17. Sayre MR, Gausche-Hill M. Conducting randomized trials in the prehospital setting. *Prehosp Emerg Care*. 6(2 Suppl):S38–47.
 18. Osterwalder JJ. Insufficient quality of research on prehospital medical emergency care—where are the major problems and solutions? *Swiss Med Wkly* 2004;134(27–28):389–94. <https://doi.org/10.2004/27/smw-10357>.
 19. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126(16):2020–35. <https://doi.org/10.1161/CIR.0b013e31826e1058>.
 20. HPCSA. Health professions council of south Africa professional board for emergency care capabilities of emergency care providers [Published 2011]. http://www.hpcsa.co.za/downloads/emergency_care/capabilites_june_2011.pdf, Accessed date: 12 February 2018.
 21. Health Systems Trust. Chapter 10: South Africa's hospital sector: old divisions and new developments. In: Padarath A, Barron P, editors. *South African Health Review 2017*. 20th ed. 2017. [Durban].
 22. Statistics SA. General Household Survey. vol. 21. 2016. [https://doi.org/10.1016/S0022-5223\(12\)00629-0](https://doi.org/10.1016/S0022-5223(12)00629-0). [Pretoria].
 23. Stassen W, Wallis L, Lambert C, Castrén M, Kurland L. Percutaneous coronary intervention still not accessible for many South Africans. *African J Emerg Med* 2017;7(3):105–7. <https://doi.org/10.1016/j.afjem.2017.04.009>.
 24. McClelland G, Pennington E, Byers S, Russell W, Lecky F. The challenges of conducting prehospital research: successes and lessons learnt from the Head Injury Transportation Straight to Neurosurgery. *Emerg Med J* 2015;1–2. <https://doi.org/10.1136/emered-2014-203870>.
 25. Pocock H, Deakin CD, Quinn T, Perkins GD, Horton J, Gates S. Human factors in prehospital research: lessons from the PARAMEDIC trial. *Emerg Med J* 2016;33(8):562–8. <https://doi.org/10.1136/emered-2015-204916>.
 26. Feldman A, Haskins R. Low-cost randomized controlled trials. Evidence-based policymaking collaborative [Published 2016]. <https://www.evidencelaborative.org/toolkits/low-cost-randomized-controlled-trials>, Accessed date: 10 June 2018.
 27. Hackland S, Stein C. Factors influencing the departure of South African advanced life support paramedics from pre-hospital operational practice. *African J Emerg Med* 2011;1:62–8. <https://doi.org/10.1016/j.afjem.2011.07.005>.
 28. Govender K, Grainger L, Naidoo R, MacDonald R. The pending loss of advanced life support paramedics in South Africa. *African J Emerg Med* 2012;2(2):59–66. <https://doi.org/10.1016/j.afjem.2011.11.001>.
 29. Iwu CG. An analysis of the reasons for staff turnover amongst paramedics in South Africa. *J Hum Ecol* 2013;43(3):225–35. <https://doi.org/10.1080/09709274.2013.11906630>.
 30. Stassen W, Wylie C, Holgate R. An online learning programme improves traumatic brain injury guideline adherence in a South African Helicopter Emergency Medical Service. *African J Emerg Med* 2015;5(4):171–5. <https://doi.org/10.1016/j.afjem.2015.05.001>.
 31. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ* 2015;350:h391.
 32. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. *BMC Med Res Methodol* 2006;6(54). <https://doi.org/10.1186/1471-2288-6-54>.
 33. Astarcioglu MA, Sen T, Kilit C, et al. Time-to-reperfusion in STEMI undergoing inter-hospital transfer using smartphone and WhatsApp messenger. *Am J Emerg Med* 2015;33(10):1382–4. <https://doi.org/10.1016/j.ajem.2015.07.029>.
 34. Miller R, Beaumont O, McGrath S. Is it now safe to use WhatsApp for clinical messaging? *Am J Surg* 2016;212(5):1032–3. <https://doi.org/10.1016/j.amjsurg.2016.06.013>.
 35. Gammelgaard A. Informed consent in acute myocardial infarction research. *J Med Philos* 2004;29(4):417–34. <https://doi.org/10.1080/03605310490503533>.
 36. Furyk JS, Lawton LD, Ting JY, McD Taylor D. Informed consent in emergency care research: an oxymoron? *Emerg Med Australas* 2017;29(1):110–2. <https://doi.org/10.1111/1742-6723.12642>.
 37. Ripley E, Ramsey C, Prorock-Ernest A, Foco R, Luckett S, Ornato JP. EMS providers and exception from informed consent research: benefits, ethics, and community consultation. *Prehosp Emerg Care*. 16(4):425–433. doi:<https://doi.org/10.3109/10903127.2012.702189>.
 38. le Roux-Kemp A. Deferred consent in emergency care research: a comparative perspective of South African regulations. *J Philos Sci Law* 2014;14:47–62.
 39. van Hoving DJ, Brysiewicz P. African emergency care providers' attitudes and practices towards research. *African J Emerg Med* 2017;7(1):9–14. <https://doi.org/10.1016/j.afjem.2017.01.003>.
 40. Harris B, Goudge J, Ataguba JE, et al. Inequities in access to health care in South Africa. *J Public Health Policy* 2011;32(S1):S102–23. <https://doi.org/10.1057/jphp.2011.35>.