Perspectives on the management of humerus fractures due to gunshot trauma: an inter- and intraobserver agreement and reliability study

By

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Declaration

I, *Esmee Wilhelmina Maria Engelmann,* 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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Abstract

Background Upper extremity fractures due to gunshot trauma are frequently treated at the level I trauma unit of Groote Schuur Hospital. There is no gold standard for the classification and management of such complex upper extremity fractures available to date and only few retrospective case studies on gunshots of the humerus were available. Interobserver agreement studies reported low levels of intra- and inter-rater reliability (IRR) for the classification of proximal humerus fractures using Neer and AO/OTA classification. The complexity of the fractures, the inconsistency of classification systems outcomes and the wide variety of treatment modalities demand evidence-based medicine.

Aim The primary aim was to assess the inter- and intraobserver agreement between surgeons in the classification and treatment of humerus fractures caused by gunshot trauma in a gunshot violence endemic area. The secondary aims were to analyse interobserver agreement with respect to debridement, removal of the bullet, the use of external fixators in patients with gunshot humerus fractures and to evaluate the effect of clinical scenarios surrounding surgical decision-making.

Methods This is an agreement study performed with a fixed panel of 32 observers who answered a set of 14 questions regarding classification and treatment by rating multiple X-ray views of a fixed set of 22 cases. The panel included junior registrars, senior registrars, orthopaedic trauma specialist and upper extremity specialists. Cases were extracted from the electronic Trauma Health Record between June 2014 and July 2016. Observers reviewed 16 midshaft and 6 proximal humerus fractures cases at 2 sessions with a 2-week interval. Descriptive statistics, Cohen's and Fleiss Kappa and rate of agreement were used to analyse data. Kappa was interpreted according to Landis and Koch guidelines.

Results There was slight yet significant overall interobserver agreement on the AO classification (k=0.20); the highest interobserver agreement ('fair') was achieved by the upper extremity specialists and senior registrars (k=0.28, 0.27). Overall interobserver reliability of agreement on preferred treatment was similar to classification agreement (k=0.18). Only trauma specialists achieved fair agreement with a significant difference compared to senior registrars and upper extremity specialists (k=0.26, 95%CI 0.21-0.32). Overall intraobserver reliability was fair for classification and moderate for treatment (k=0.39, 0.42). There was fair overall agreement on debridement of the wound (k=0.26) and removal of the bullet (k=0.31) and close to poor agreement for the use of temporary external fixators (k=0.03). Vascular injury was rated as influential factor on decision-making by the majority of observers (53.7%), followed by bilateral (37.1%) and other fractures (26.8%).

Conclusions This is the first intra- and interobserver agreement study that evaluated classification and treatment of gunshot humerus fractures in the light of a broader spectrum of patient- and fracture-related factors. Consistent with previous studies, there was low interobserver agreement for the classification and treatment of proximal humerus fractures, thereby contributing to the field of knowledge with specific evidence regarding gunshot trauma. Future research should further assess predictive factors in

surgical decision-making and analyse global preferences in order to develop evidence-based classification and treatment guidelines for the management of patients with humerus fractures.

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Surgeons who knew about this study prior to the start, including Dr T Mukabeta and Professor S Roche, were excluded from participation to the sessions to prevent observer bias. All observers are acknowledged for their attendance, input and responses: Dr S Pretorius, Dr N Kruger, Dr I Koller, Dr JP Duplessis, Dr M Roussot, Dr J Kawuta, Dr A Swan, Dr J Charilou, Dr Z Moonda, Dr C Bezuidenhout, Dr S Swanepoel, Dr R Magampa, Dr S Rhoma, Dr J Mccaul, Dr M Workman, Dr W Mugla, Dr W Nkomo, Dr V Boskovic, Dr T Duma, Dr S Maqungo, Dr D Mguire, Dr N Kruger, Dr G Mccollum, Dr B Bernstein, Dr R Dachs, Dr M Held, Dr Y De Wet, Dr C Steyn, Dr M Mulder and Dr B Grey.

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Abbreviations

eTHR	electronic Trauma Health Database
HREC	Health Research Ethics Council
AO/OTA	Arbeitsgemeinschaft fur Osteosynthesefragen and Orthopaedic Trauma Association
AP	anteroposterior
HUMMER	HUMeral shaft fractures: MEasuring Recovery after operative versus non-operative treatment
PROFHER	PROximal Fracture of the Humerus: Evaluation by Randomisation trial
IRA	Inter-rater agreement
IRR	Inter-rater reliability
ICC	Intraclass correlation coefficient
ORIF	Open Reduction Internal Fixation

Chapter 1: Introduction and literature review

Objectives of literature review

The main objective of the literature review was to provide a structured and comprehensive overview of the evidence available in the literature. This evidence includes up to date information on both the global and local context and relevance of this dissertation; the types of humerus fractures and different classification systems; the current options for management of these fractures; background information regarding the agreement and reliability of multiple observers; and the use of statistics to assess the influence of factors on clinical decision-making. By summarizing and interpreting the existing knowledge, we aim to identify research gaps and areas of interest that require further attention in the future. This introductory chapter functions as motivation for the rationale for the dissertation and is concluded with the aims and hypotheses of the study.

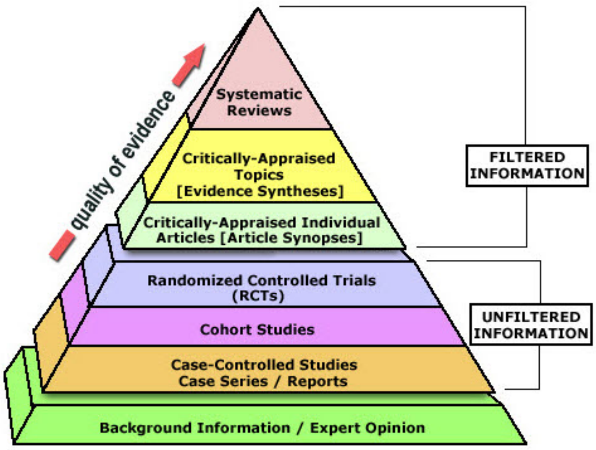

Figure 1: Pyramid of evidence-based medicine, copyright 2006 Trustees of Darmouth College and Yale University. By Jan Glover, David Izzo, Karen Odato, Lei Wang.

Search strategy

Different types and levels of evidence were searched, varying in quality as visualised in the evidence-based medicine pyramid (figure 1). We identified and analysed articles on humerus fractures in adults due to ballistic trauma published between 1943 and 2017 in all databases and journals in Thomson Reuters' Web of Knowledge covering all levels of evidence, including PubMed for primarily unfiltered information and the Cochrane Collaboration Database for filtered information. All articles with the primary focus on humerus fractures were included and subdivided between firearm injuries, other penetrating trauma and non-penetrating trauma. Gunshot injuries caused by civilian violence as well as injuries from military conflicts and war were included. The research for this dissertation was conducted at Groote Schuur Hospital, which implies children could not be cases and thus we applied an age restriction of at least older than 18 years for patients evaluated in studies. There was no language restriction. Studies that focused on other injuries or other anatomical structures in a higher degree than on humerus fractures due to gunshot trauma were excluded. For example, we excluded one article that concerned the management of upper extremity fractures due to gunshot trauma with only 8 cases of humerus fractures and 31 cases of other fractures such as scapula, radius and ulna.

The following Boolean queries with the asterisk extending the search to every possible ending of the words were applied: (upper AND (limb OR extremit*) AND fracture*), (humer* AND fractur*), both alone and through AND (gunshot* OR firearm OR armed OR violence OR weapon*); (classif* AND fractur*), alone and with AND (upper extremit* upper limb OR long bone* OR humerus*); ((observer OR rater) AND (reliability OR agree* OR correlation) AND (humerus* OR upper extremit* OR upper limb)). These queries were run as title and/or abstract searches.

This search strategy resulted in 302 hits, of which 49 were eventually included after a multiple-step approach as demonstrated in figure 2. Exclusion was based on the focus of the publication, age of patients and number of patients in case series with a threshold of at least ten patients. For example, one article was excluded because it focused on the classification of proximal humerus fractures in the light of the natural history of these fractures rather than on the classification systems used to identify the fracture pattern and to support surgical planning. In the summary of literature, we primarily focused on the interpretation of literature on humerus fractures due to gunshot trauma specifically since that is the focus of this dissertation.

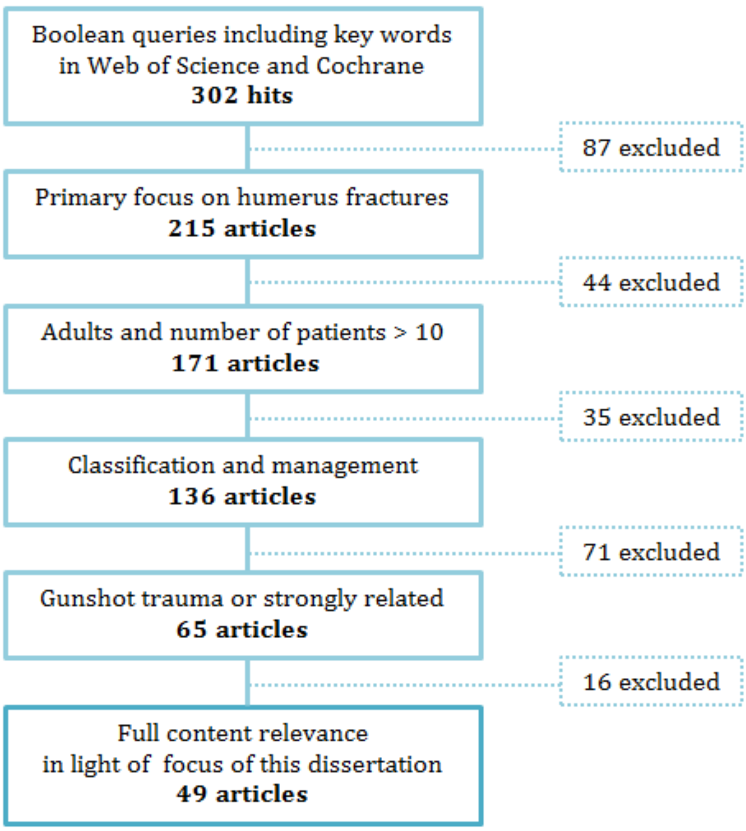

Figure 2: Flow chart of search strategy

Next to using sources to find clinical and scientific evidence on the topic, we also searched through other sources including reports published by the United Nations on armed violence worldwide and books on intra-rater agreement and reliability theories and statistical analysis. With respect to management, we analysed the most recent protocols and guidelines on the topics as published on for example UpToDate. The online clinical trials registry including publicly and privately supported clinical studies across the world was searched for relevant closed, active and future studies (clinicaltrials.gov).

Summary of literature

Global and local relevance
Today, armed violence constitutes one of the greatest global health challenges[1,2]. This was stressed once again in a recent publication by the Geneva Declaration on Armed Violence and Development, a diplomatic initiative endorsed by over 100 states to fight against armed violence as an obstacle to successful development[1]. Civilian gunshot-related violence still kills over a thousand people and injures millions of others worldwide every day[1-3]. The growing burden of gunshot injuries demands evidence-based and protocolled ballistic trauma management. Within the patient population of ballistic injuries, musculoskeletal injuries constitute a unique group in terms of demographics, injury patterns, management, surgical techniques and clinical outcomes[4-8].

Although firearm-related homicide rates are low in first world countries and declining in many developing countries, gunshot injuries remain a severe and increasing burden to trauma services in various parts of Africa[1-3,9-11]. The extremely high levels of various types of interpersonal violence in the country result in many deaths and more than a thousand ballistic injuries presented yearly at the level I trauma unit of Groote Schuur Hospital in Cape Town according to findings from the electronic Trauma Health Database (HREC 685/2016). Approximately one third of these have orthopaedic injuries that have a significant socioeconomic impact and impose a severe burden on the trauma services of the hospital.

Upper extremity injuries are common and intra-articular ballistic trauma in particular tends to have a severe impact on morbidity[12-16]. In the high-burden urban public hospital in Cape Town, South Africa, upper extremity fractures and associated neurovascular damage are frequently seen at the level I trauma unit of Groote Schuur Hospital. There is no gold standard for the classification and management of comminuted upper extremity fractures caused by gunshots[12,15,16]. There are only few studies on gunshots of the upper extremity available; these are relatively old, retrospective case series of small sample sizes from Western countries[12-14,16-19].

Humerus fractures
The humerus is the largest bone in the upper limb. Humerus fractures can be divided into proximal, midshaft (or diaphyseal,) or distal. The proximal humerus is the part that articulates with the glenoid of the scapula to make the shoulder joint. Several muscles and tendons, such as those of the rotator cuff, are attached at different anatomical structures to stabilise the glenohumeral articulation and provide the broad range of motion[36,37]. The axillary artery accounts for the main blood supply to the proximal humerus. Distal to the anatomical neck, the anterior and posterior humeral circumflex

arteries originate, which then travel proximally to provide blood supply to the humeral head. Proximal humerus fractures can thus damage the blood supply and lead to avascular necrosis of the head. Other complications may occur due to the neurological injuries given the close relation between the humerus and the axillary nerve and brachial plexus. In practice, the axillary and subscapular nerves are most frequently damaged[39]. Median and ulnar nerve injuries are found to be uncommon[36,37]. The humeral shaft supplies an area of attachment for powerful muscles, including the deltoid muscle. Its blood supply is provided by the axillary and brachial artery and can be damaged by fracture fragments or displacement of shaft fragments. Neurological injuries can occur as a result of displacement of diaphyseal or distal fractures with involvement of the radial nerve. The distal humerus is near the elbow where the humerus articulates with the radius and ulna. We regard these injuries as different entities and they will therefore not be discussed further.

In a prospective analysis of 1027 proximal humerus fractures, Court-Brown et al. estimated an incidence of proximal humerus fractures of 4 to 5%[40]. At a later follow-up stage, they found that midshaft humerus fractures accounted for 2% of 5953 fractures in adults[41]. According to literature, a fall from standing is the most common injury mechanism with approximately 90% of all humerus fractures[36,37]. When a patient is suspected to have a proximal humerus fracture, the standard series of radiographs should include a true anteroposterior (AP) view, an axillary view and a scapular Y-view. Midshaft humerus fractures are generally caused by trauma such as a bending force or high-velocity external forces[36,37]. Anteroposterior and lateral radiographs are indicated to assess the amount of angulation or displacement.

Classification

A number of classification systems have been designed to describe fractures to the upper extremity. Accurate and reliable fracture characterisation is important in deciding whether or not to operate and in the selection of the surgical modality[45]. According to previous findings from the electronic Trauma Health Database, most upper extremity fractures due to gunshots are complex, irregular and multi-fragmentary with a large fracture length and many tiny fracture fragments (figure 3 and Engelmann, submitted for publication; HREC 685/2016). With regard to injury classification, our literature search shows that the classification of fractures varies widely among research groups worldwide. The Arbeitsgemeinschaft für Osteosynthesefragen and Orthopaedic Trauma Association (AO/OTA) developed a classification for fractures and dislocations of all long bones. It is often described as a comprehensive, systematic classification system that is amongst others used for midshaft and distal humerus classification (Appendix 3). Another classification system for proximal humerus fractures is the Neer classification, which is based on the anatomical relationship between the anatomical neck, the surgical neck, the greater tuberosity and the lesser tuberosity[36]. Fractures are classified on the basis of displacement of segments, defined as angulation of more than 45 degrees or more than 1 centimetre of displacement from the anatomic position. Other studies on upper extremity ballistic trauma used the injury location, bullet velocity, Gustilo-Anderson classification, types of involved tissue or they did not use a classification system at all[13,14,16,18,19].

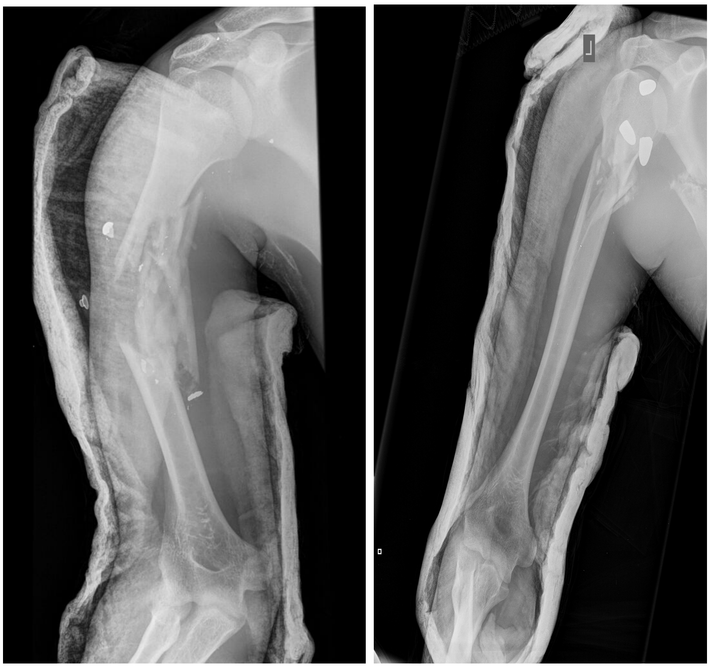

Figure 3: Midshaft (left) and proximal (right) humerus fracture caused by gunshot trauma

Foroohar et al. and Bruinsma et al. demonstrated that intra- and inter-rater reliability (IRR) for the classification of proximal humerus fractures using Neer and AO was limited[28,9]. It was also concluded that the additional use of two-dimensional CT scans did not improve the IRR of classification systems[29,30]. A group of Swiss trauma surgeons and radiologists did not agree; they found moderate interobserver reliability in Neer and AO/OTA classification with radiographs and two-dimensional CT scans but found a significant increase in reliability after stereo visualisation of three-dimensional volume-rendered CT scans[44]. This imaging modality may be of particular interest in the classification of complex fractures of the proximal humerus, such as those multi-fragmentary comminuted fractures caused by gunshot trauma. Over the past years, several attempts have been made to design a new, appropriate classification system for the proximal humerus fracture. Mutch et al. stated that their morphological division of humerus fractures into three categories, namely avulsion, split and depression, resulted in a higher inter- and intraobserver reliability than Neer and AO/OTA[43]. A three-dimensional system consisting of five basic types depicted usefulness for surgeons in guiding anatomical reconstruction[47].

A geographical analysis of the articles on classification systems showed that the analyses and new classification system designs all originated from North American or European countries. No studies or ideas from high trauma burden countries were published. Despite efforts by various research groups, no validated classification tool other than Neer and AO/OTA was put into clinical practice up to date[21,22].

Management

Upper extremity gunshot injuries are generally treated either conservatively using plaster or splint, or surgically with open reduction internal fixation (ORIF), intramedullary nails and external fixators. Following irrigation and debridement, ORIF techniques may be subdivided further in compression, neutralising and bridging plates with locking or non-locking screws. Wounds can be debrided and the bullet may or may not be removed. The complexity of the fractures, the inconsistency of classification systems outcomes and the wide variety of treatment modalities increase the need for evidence-based medicine. However, there are no guidelines or evidence-based protocols concerning the management and therapeutic options for the complex, often multi-fragmentary upper extremity fractures caused by gunshot trauma available in literature[50].

The management of proximal humerus fractures varies widely[24]. A non-surgical approach to single fragment fractures was suggested by an observational case series of 507 patients treated conservatively[51]. In case of displaced or multi-fragmentary fractures, operative management may be indicated[36,37]. Neurovascular injuries and fracture dislocations demand for acute (surgical) care[36,37]. Multiple systematic reviews on non-traumatic fractures reported contrasting conclusions, but agreed on the fact that there is insufficient evidence available to decide which management options are best for different types of proximal humerus fractures[36,37]. In the randomized PROFHER trial that concentrates on displaced proximal fractures yet did not include gunshot wound patients, no difference in overall shoulder function was found between surgical and non-surgical treatment after a two-year follow-up period of patients without clear indications for surgery[52]. The latest update of a Cochrane review on interventions for the treatment of these fractures once more stressed the fact that there is insufficient evidence to inform the management, even for specific fracture types[25,38]. According to the authors, it is unclear whether surgery results in better functional outcomes yet it was associated with a higher risk of complications and need for further surgery[24]. The optimal approach should thus be chosen only after careful consideration on an individual basis.

The majority of humeral shaft fractures is probably treated conservatively according to Bassett and Gosler[25,36,37,]. When surgical treatment is indicated, internal fixation with plates used to be preferred over nailing for most patients[53]. More recently however, one randomised controlled trial has shown that intramedullary nailing may be better than compression plating because it was associated with a shorter union time and lower incidence of complications such as infection[55]. No differences between nailing and plating were found with respect to union rate and functional outcome[55]. A number of research groups has aimed to compare operative versus non-operative treatment of such fractures. Systematic reviews including high quality trials have repeatedly shown that there is no clear evidence for surgery or bracing as optimal management for non-displaced midshaft fractures[36]. Two Cochrane reviews on the treatment of midshaft humerus fractures were published in 2012 and 2016[25,38]. Similar to the proximal humerus fractures, there was insufficient high-quality evidence available to help inform the management. Surgical intervention was not proven to be superior over conservative management in upper extremity fractures in these reviews.

Current trials on humeral shaft fractures aiming to provide new insights into this critical issue include HUMMER, a Dutch multicentre comparative observational study measuring recovery after operative versus non-operative treatment and a Brazilian trial comparing outcomes of bridge plating to those of a functional brace[50]. Multiple single-centre clinical trials are currently recruiting to compare surgical versus non-operative management in the elderly population. No results are published yet.

No clinical trials focusing on humerus fractures caused by firearm or even other penetrating trauma have been conducted yet. Observational studies from Europe and USA on humerus fractures due to firearms seem to regard external fixation as the best management modality[10,12,13,15-18]. A previous retrospective case series by the Orthoballistics research group depicted that many fractures in Groote Schuur Hospital were managed conservatively (HREC 685/2016, submitted for publication). Other aspect of management, such as whether or not to debride, remove the bullet or use a temporary external fixator, have neither been studied in high-quality settings nor included in management protocols. This could suggest that patients with humerus fractures due to gunshot trauma may in practice be treated on a case-by-case basis.

Observer reliability
In order to perform this study, the methods and outcome measures should be framed and defined. Although the term agreement and reliability are frequently used interchangeably, they are technically and fundamentally different. Inter-rater agreement (IRA) indices assess the extent to which the responses of two or more independent observers are concordant or identical[27]. It can be calculated as the number of concordant responses divided by the total number of responses times 100%.

Reliability is a measure of consistency or degree of dependability. Inter-rater reliability indices assess the extent to which observers consistently distinguish between different responses; it is associated with the extent of variability and error inherent to measurement[27]. Reliability is thus calculated as the observer variability divided by the observer variability plus the measurement error[27]. IRR is the measurement of the extent to which observers assign the same score to the same variable. It can be tested by the kappa statistic, developed by Jacob Cohen in 1960 to account for the possibility that raters actually guess on at least some variables due to uncertainty[26]. Like most correlation statistics, the kappa can range from -1 to +1 and values closest to 1 indicate good correlation[26]. It must be noted that the kappa value does not relate to the best treatment. For instance, the kappa may approach 1 while the management chosen by the observers may in fact not be the correct technique or optimal choice in practice. Cohen's kappa was designed for the situation in which two observers rate any number of, for example, X-rays. In the case of more than two observers, intraclass correlation coefficients (ICC) or Fleiss' kappa are used as test statistic[28,33,55]. Fleiss' kappa is a statistical measure that was designed in 1971 to expand the use of kappa-like statistics for interobserver reliability of agreement. It assesses the reliability between a fixed number of observers that rate a fixed number of items categorically[55]. Similar to Cohen's kappa, no weighting is used and the categories are assumed to be unordered. The ability of an observer to reproduce outcomes under the same test conditions is referred to as intra-rater reliability[28]. To test this, ICC is used for continuous variables and a kappa coefficient is preferred for nominal data[28].

Predictive analytics
Factors influencing the clinical decision-making of operative treatment for gunshot fractures are debated[31]. A recent interobserver reliability study on proximal humeral fractures showed that observers who received patient information recommended conservative treatment more often than those who did not have this information[31]. The

most important details were (older) patient age, fracture mechanism and region of practice[31]. Other agreement and reliability studies did not assess clinical scenarios.

Research gaps

The interpretation of the existing knowledge has led to the identification of a number of research gaps concerning the perspectives on classification and management of humerus fractures due to gunshot trauma. Firstly, in the context of global health and surgery and based on the worldwide distribution of ballistic trauma, there is a lack of contributions to the field from African countries. Secondly, we believe that there is a lack of knowledge regarding classification systems for humerus fractures caused by high energy trauma mechanisms. The literature review demonstrated that studies about humerus fractures in general reported low reliability and agreement of AO/OTA and Neer's among large groups of observers. Although different research groups have attempted to develop new classification systems, none of them has specifically focused on fractures due to gunshot trauma or any other trauma mechanism so far. In fact, there is only a handful of studies available that even describe such complicated, multifragmentary fractures. Thirdly, we found that intra- and interobserver reliability studies were conducted on proximal humerus fractures, however, these did not include fractures caused by high energy trauma. In the fourth place, many articles focusing on gunshot humerus injuries repeatedly emphasize the complexity and challenges of management of fractures, yet there are no studies that investigate the rationale and clinical decision-making of surgeons treating such cases. Finally, there is an important research gap in the pace and quality of clinical trials that focus on the management of humerus fractures.

Aims and hypotheses

This inter- and intraobserver reliability study may once more identify common and important denominators in the classification and management of humerus fractures caused by gunshot trauma. Next to intra- and interobserver agreement and reliability, we aim to obtain insight into the background of a surgeon's choice for treatment.

The primary aim is thus to assess the inter- and intraobserver reliability between surgeons in the classification and treatment of humerus fractures caused by gunshot trauma in an armed violence endemic area. We aim to test the null hypothesis that interobserver reliability is low for the AO classification and high for treatment. We also hypothesise that there is no difference in interobserver reliability between different types of surgeons, and that intraobserver reliability is high. The main research question therefore is: What is the level of inter- and intraobserver agreement and reliability in the injury classification and management of patients with humerus gunshot fractures?

The secondary research aims were to analyse interobserver agreement with respect to debridement, removal of the bullet and the use of external fixators in patients with gunshot humerus fractures and to evaluate the effect of clinical scenarios on surgical decision-making.

Chapter 2: Methods

Study design
This is an agreement and reliability study performed with a panel of observers who answered a fixed set of questions regarding classification and treatment by rating multiple view X-rays of a fixed number of cases.

Study population
A cohort of practicing surgeons, referred to as observer panel, reviewed radiographs and answered survey questions. The panel included junior registrars, senior registrars, orthopaedic trauma specialists and upper extremity specialists. An upper extremity specialist was defined as a surgeon with fellowship training and a practice focus on the upper extremity whose practice includes the surgical management of gunshot fractures. An orthopaedic trauma specialist was defined as a surgeon with specific training in traumatic orthopaedic injuries, including gunshot fractures. A junior registrar has less than 2 years of training experience; a senior registrar has more than 2 years of experience. Next to different specialisations, the observers had various degrees of clinical experience that were defined as years of independent practice. Based on previous studies and our own power analysis, we included 32 observers. The observer demographics are described in table 1.

We included 22 cases of patients with humerus fractures due to gunshot trauma. Sixteen of these were midshaft or diaphyseal fractures and six were proximal humerus fractures. Patients with distal humerus fractures were not eligible for inclusion. Proximal humerus fractures were included because they were studied in an intra- and interobserver study before and because they are relatively rare and complex. Midshaft humerus fractures were included because they occur commonly after gunshot trauma and because we assumed a variety of treatment modalities was used in practice. Given the anatomical structures and proximity of the distal humerus to the forearm, we regarded the distal humerus as a different entity in terms of classification and management. The same 22 cases were presented to the same 32 observers for review in two different sessions.

Recruitment
We invited both registrars and orthopaedic surgeons of the orthopaedic department of Groote Schuur Hospital, as well as specialized surgeons from private clinics. This allowed us to compare intra- and interobserver reliability between the public and private practice. Registrars that had knowledge about this study prior to the start and the supervisor were excluded from participation to prevent observer bias (Acknowledgement).

We constructed a list of consecutive patients with humerus fractures due to gunshot trauma who presented at the Trauma Unit at Groote Schuur Hospital and were thus included in the electronic Trauma Health Record (eTHR). The eTHR is an iPad app with built-in clinical checklists and injury severity scoring designed to collect and analyse data in admissions, operations and discharges. We aimed for 32 consecutive cases (16 midshaft and 16 proximal) but this proved unsuccessful due to availability of data from the eTHR and the low incidence of proximal humerus fractures. Patients were included in a consecutive order, starting from July 2014 when the eTHR was used for every trauma patient admitted at Groote Schuur Hospital. The most recent patient dated from June 2016 and no data was available afterwards. This resulted in a total sample size of 22 cases (16 midshaft, 6 proximal). All patients had multiple view X-rays available.

Research procedures

Two evening sessions were organised for the observers to rate the cases collectively at an interval of two weeks. This time span had been used in previous reliability studies. Each observer answered the following three yes-or-no questions for each of the twenty-two humeral fractures: (1) Would you debride the wound? (2) Would you remove the bullet? (3) Would you use a temporary external fixator? Next, the observer classified the fracture according to the AO system and indicated his or her preferred treatment (conservative, intramedullary nail, open reduction and internal fixation or external fixator). The original idea to further divide the open reduction and internal fixation option in compression or neutralizing plating versus bridge plating followed by locking or non-locking screws failed as less than one tenth of the observers indicated the details of their ORIF preference.

During the sessions, a Powerpoint presentation was used to show the cases. The observers were given a brief review of the AO/OTA classification on a sheet and no other information was provided. They were given one question sheet and one set of answer sheets to rate the cases (Appendix 1 and 2).

Data safety

Only essential demographic information and required images of the injury were collected. The data was stored on the investigators' laptop and on the university computer account. All storage facilities were password protected and kept locked away when not in use. All personal data was be deleted from the database and X-rays and a numerical code was assigned to each case. Observers in the review panel were anonymous too and the results cannot be traced back to individual observers. Informed consent was given by all observers prior to participation in the study (Appendix 1, signed forms attached separately).

By conducting the study offline, we minimised the chance of knowledge bias by for example using the internet or books when the survey would have been conducted digitally. Since the session were held at the department in Groote Schuur Hospital, this option best guaranteed data safety because we did not have to rely on online survey programs or data storage systems.

Statistical analysis

Descriptive statistics were used to describe the observer demographics. Normally distributed continuous data was summarized by mean and 95% confidence intervals and non-normally distributed continuous data by median and interquartile range. Interobserver reliability of agreement was determined by the use of the multi-rater kappa as described by Shrout and Fleiss. This statistical value incorporates both reliability and agreement. Two-tailed tests were used to calculate z-statistics and confidence intervals at $\alpha = 0.05$. We used the guidelines of Landis and Koch for kappa value interpretation (Appendix 4)[32]. These categories are arbitrary yet well recognized in orthopaedic literature[29-32]. Statistical differences between individual kappa values were regarded significant when the upper and lower boundaries of 95% confidence intervals did not overlap. Since no continuous variables were used in this study, the assumptions of reliability correlation coefficients were not met and ICC was not used[34].

Factors associated with choice for treatment and reliability were meant to be analysed using binomial logistic regression, however, this analysis proved unsuccessful as only four observers indicated the effect of variables on their choice of treatment. Consequently, there was insufficient information available to assess the dependent variable against a number of independent variables or predictors. The influence of clinical scenarios on the surgeon's choice of treatment was alternatively analysed using the average number of observers per case who indicated that a variable would change their treatment, converted into a proportion of the total number of observers. The IBM SPSS Statistics software was used to collect data and analyse results (version 22, IBM Corporation, Armonk, New York).

Power calculation

The use and relevance of power calculations for sample size and kappa values was subject to discussion amongst statisticians[34-36]. An argument in favour of power analysis was the potential to guarantee validity of results. An argument against looking for statistically significant values of kappa was the fact that kappa may be highly significant, but still indicate low reliability. The smaller the relative error or the difference between overall and chance reliability probabilities, the higher the sample size required.

A power analysis was run to estimate the minimum sample size for two-sided tests and confidence intervals (nQuery Advisor software, version 7.0, Statistical Solutions, Saugus, Massachusetts). The required sample size was 5 to 49 cases, depending on the desired power, expected proportion of successes and the width of the confidence interval. For example, it was calculated that for a two-sided test with a significance level of 0.05, we needed 16 cases to yield 80% power in detecting a 0.02 difference in kappa value. The power analysis indicated that we had to recruit 24 observers and 16 cases. Given the chance of loss of no-shows at one of the sessions and the related loss to follow-up, we invited a higher number observers and also included more cases to increase power[35,36].

Chapter 3: Results

Observer demographics
We recruited 10 junior registrars, 5 senior registrars, 8 orthopaedic trauma specialists, 8 upper extremity specialists and 1 other surgeon (lower limb specialist). There was only one female observer. Most observers practiced in a public hospital: 18 of them worked in Groote Schuur Hospital, 1 in Tygerberg Hospital and 1 in Paarl. About one fifth of observers (N=7, 21.9%) worked in private practice, of which 4 worked for Mediclinic, 2 for Netcare and 1 in Vincent Palloti. Five observers (15.6%) worked in both private and public practice, in Groote Schuur Hospital and in Somerset Hospital or one of the other private clinics mentioned above. The mean age of observers was 38.3 years with a standard deviation of 5.5 years and the median age was 38 years with a range of 25 years from 31 to 56 years (IQR 6.8). The age distribution is demonstrated in figure 4. The majority of observers had been in independent practice for 0 to 5 years (N=22, 68.8%). Six observers had more than 10 years of independent clinical experience (15.6%). About half of the observers supervised trainees in the operating room (N=15, 46.8%), including all trauma specialists (N=8). The observer demographics are displayed in table 1 and 2.

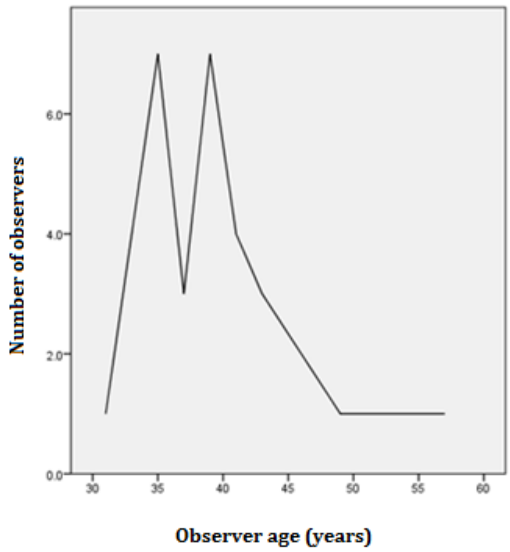

Figure 4: Age distribution of observers (N=32)

Five observers (15.6%) were lost to follow-up: one junior registrar, two trauma specialists and two upper extremity specialists. They were not included in any intra-rater analysis.

Table 1: Observer demographics

	Total in N (%)
Sex	
Male	31 (96.8)
Female	1 (3.1)
Hospital	
Public	20 (62.5)
Private	7 (21.9)
Both	5 (15.6)
Specialisation	
Junior registrar	10 (31.2)
Senior registrar	5 (15.6)
Trauma specialist	8 (25.0)
Upper extremity specialist	8 (25.0)
Other	1 (3.1)
Years in independent practice	
0-5	22 (68.8)
6-10	5 (15.6)
11-20	4 (12.5)
21-30	1 (3.1)
Supervises trainees in theatre	
Yes	15 (46.8)
No	17 (53.1)

Table 2: Demographics specified per observer group

	Junior (N=10)	Senior (N=5)	Trauma (N=8)	Upper extremity (N=8)
Age (mean $\pm$ SD)	34.7 $\pm$ 2.4	36 $\pm$ 3.7	42 $\pm$ 7.4	40.6 $\pm$ 4.3
Hospital				
Public	10	5	2	3
Private	0	0	2	4
Both	0	0	4	1
Independent practice				
0-5	9	3	4	5
6-10	1	1	1	2
11-20	0	1	2	1
21-30	0	0	1	0
Supervises trainees				
Yes	3	0	8	3
No	7	5	0	5

Classification

There was slight yet significant overall interobserver agreement on the AO classification, as displayed in table 3. Junior registrars (N=10) and trauma specialists (N=8) were found to have the lowest interobserver agreement indicated by kappa values of 0.15 and 0.12, respectively. The highest interobserver agreement values was achieved by the upper extremity specialists (k=0.28), followed by the senior registrars (k=0.27). These groups both agreed significantly more than the other groups, as proven by the non-overlapping confidence intervals at $p<0.05$ (* in table 3). A difference was found between midshaft and proximal fractures with k=0.18 corresponding to slight agreement for midshaft fractures and 0.21 for proximal fractures, not statistically significant due to overlapping confidence intervals at $p<0.05$.

Table 3: Interobserver agreement on AO classification according to specialisation

	k	Agreement	SE	95% CI	p
Overall	0.20	Slight	0.00	0.20, 0.21	0.00
Specialisation					
Junior	0.15	Slight	0.01	0.13, 0.17	0.00
Senior	0.27	Fair	0.02	0.22, 0.32	0.00*
Trauma	0.12	Slight	0.01	0.09, 0.15	0.00
Upper extremity	0.28	Fair	0.02	0.24, 0.31	0.00*

k = Fleiss' kappa, SE = standard error, CI = confidence interval. *Significant

Intraobserver reliability of agreement according to observer specialisation and demographics is shown in table 4. As with interobserver analysis, no statistical difference was found between the two types of fractures. Overall intraobserver reliability was fair (mean kappa =0.39, mean standard error = 0.11) and a number of groups demonstrated moderate and close to substantial agreement. Senior registrars and upper extremity specialists achieved significantly higher intra-rater reliability than the other two groups ($p<0.05$). The highest intraobserver reliability as indicated by mean and median kappa was achieved by the upper extremity specialists: moderate and close to substantial agreement at mean kappa 0.56 (SE=0.13) and median 0.58 (IQR=0.24). With respect to type of hospital and experience, surgeons practicing in private hospitals and surgeons with 5 or more years of independent practice had higher intraobserver agreement, which was not statistically significant. Observers who supervised trainees in the operating room did not have better agreement than those who did not (k=0.37, k=0.41, overlapping 95% CI at $p>0.05$).

Table 4: Intraobserver reliability of agreement on AO classification according to observer demographics

	Mean k (SE)	Median k (IQR)	Agreement
Overall	0.39 (0.11)	0.40 (0.31)	Fair
Specialisation			
Junior	0.26 (0.10)	0.27 (0.31)	Fair
Senior	0.45 (0.12)	0.42 (0.49)	Moderate
Trauma	0.37 (0.12)	0.35 (0.18)	Fair
Upper extremity	0.56 (0.13)	0.58 (0.24)	Moderate
Hospital			
Public	0.35 (0.11)	0.34 (0.34)	Fair
Private	0.52 (0.13)	0.43 (0.25)	Moderate
Both	0.34 (0.11)	0.32 (0.24)	Fair
Independent practice			
< 5 years	0.37 (0.11)	0.39 (0.33)	Fair
≥ 5 years	0.45 (0.12)	0.41 (0.35)	Moderate

k = Cohen's kappa, SE = standard error, IQR = interquartile range.

Treatment

Overall interobserver reliability of agreement on preferred treatment was similar to the overall interobserver reliability on classification (k = 0.18). Only trauma specialists achieved fair agreement with a significant difference compared to senior registrars and upper extremity specialists at $p<0.05$ (table 5). The agreement of senior registrars was poor and close to chance agreement. Both midshaft and proximal fractures were rated with slight agreement at kappa 0.18 (95% CI = 0.16, 0.20). No difference between private and public practitioners was found at kappa = 0.19 and 0.16 respectively, overlapping confidence intervals at $p<0.05$.

Table 5: Interobserver reliability of agreement on preferred treatment

	k	Agreement	SE	95% CI	p
Overall	0.18	Slight	0.01	0.17, 0.20	0.00
Specialisation					
Junior	0.18	Slight	0.02	0.14, 0.23	0.00
Senior	0.04	Slight	0.05	-0.06, 0.13	0.47
Trauma	0.26	Fair	0.03	0.21, 0.32	0.00
Upper extremity	0.14	Slight	0.03	0.08, 0.20	0.00

Intra-rater reliability demonstrated more differences between observers (table 6). Overall intra-rater agreement was moderate at a mean Cohen's kappa of 0.42, median kappa of 0.39. The lowest kappa was -0.39, which was lower than chance agreement, and one observer chose the same treatment for all cases at the two sessions (kappa = 1.00). Trauma specialists had the best agreement, significantly different from the other groups, followed by upper extremity specialists. There were no major differences in the type of practice or years of independent practice. Observers who supervised trainees in the operating room did not have better agreement than those who did not (k=0.43, k=0.42, overlapping 95% CI at $p<0.05$).

Table 6: Intraobserver reliability of agreement on treatment according to observer demographics

	Mean k (SE)	Median k (IQR)	Agreement
Overall	0.42 (0.14)	0.39 (0.49)	Moderate
Specialisation			
Junior	0.35 (0.15)	0.28 (0.45)	Fair
Senior	0.41 (0.16)	0.31 (0.50)	Fair
Trauma	0.57 (0.15)	0.57 (0.33)	Moderate
Upper extremity	0.42 (0.10)	0.36 (0.66)	Fair to moderate
Practice			
Public	0.37 (0.15)	0.31 (0.42)	Fair
Private	0.46 (0.13)	0.39 (0.52)	Fair to moderate
Both	0.52 (0.14)	0.54 (0.47)	Moderate
Independent practice			
< 5 years	0.39 (0.15)	0.33 (0.43)	Fair
> 5 years	0.50 (0.13)	0.47 (0.50)	Moderate

Secondary aims

Observers had moderate overall agreement on debridement of the wound and removal of the bullet (table 7). The agreement for these management options was significantly better than the slight agreement for the use of temporary external fixators. The best agreement was achieved for the removal of the bullet in cases of proximal humerus fractures, with moderate agreement at Fleiss' kappa of 0.43, SE 0.02 and 95% confidence interval of 0.40-0.47 at $p<0.01$ compared to fair agreement at k=0.21, SE 0.01, 95% CI 0.18-0.23 at $p<0.01$. For debridement and the use of temporary external fixators, there was no difference between midshaft and proximal fractures.

Table 7: Overall interobserver agreement related to secondary aims

	k	Agreement	SE	95% CI	p
Debridement	0.26	Fair	0.01	0.25, 0.28	0.00
Remove bullet	0.31	Fair	0.01	0.29, 0.33	0.00
External fixator	0.03	Slight	0.01	0.01, 0.05	0.01

Observers were asked whether additional patient information would influence their decision-making regarding the preferred treatment (table 8). All observers indicated that the patient's sex does not influence their choice of treatment in any of the cases. For both midshaft and proximal fractures, vascular injury was the most influential factor as two-thirds of observers indicated for midshaft fractures and close to one-third of observers for proximal factors. Bilateral fractures and other fractures also influenced treatment for midshaft fractures more than for proximal fractures. Hand dominance, neurological injury and employment status were identified as influential factors by only 2 to 4 observers on average (4.7-9.8%).

Table 8: Additional information used by the observers for decision-making regarding treatment

Parameters	Overall (%, N)	Midshaft (%, N)	Proximal (%, N)
Sex	0.0 (0)	0.0 (0)	0.0 (0)
Employment status	9.8 (3.1)	11.5 (3.7)	5.2 (1.7)
Hand dominance	4.7 (1.5)	4.7 (1.5)	4.7 (1.5)
Bilateral fractures	37.1 (11.9)	44.1 (14.1)	18.2 (5.8)
Vascular injury	53.7 (17.1)	63.3 (20.3)	28.1 (9.0)
Neurological injury	6.3 (2.0)	7.6 (2.4)	2.6 (0.8)
Other fractures	26.8 (8.6)	36.9 (11.8)	14.1 (4.5)

N = average number of observers per case, % = of total observers.

An average of 25.3 observers per case considered the information available of sufficient quality to use it for their decision-making, which corresponds to 79.0% of observers. Observers rated the quality of available information for proximal fractures lower than for the cases with midshaft fractures, at 16.3 observers per case and 51.0% of observers for proximal fractures versus 28.6 observers per case and 89.4% of total number of observers for midshaft fractures.

In terms of compliance, the most frequently skipped question was the classification at a response rate of 38 to 100%. The response rate range for the other thirteen questions was 94-100%.

Chapter 4: Discussion

Classification

Most observers were surgeons in training, the majority of observers had been in independent practice for 0 to 5 years and about half of the observers supervised trainees in the operating room. The group of trauma specialists were most experienced based on age, years of independent practice and supervision of trainees. There was only slight yet significant overall interobserver agreement on the AO classification and the highest interobserver agreement ('fair') was achieved by the upper extremity specialists and senior registrars. This may indicate these two groups are best trained in or familiar with using the AO classification, perhaps because the classification is designed for long bone fractures and trauma specialists may deal with a greater amount of other injuries.

Our slight to fair overall agreement on midshaft and proximal humerus fracture classification is consistent with the findings of Foroohar et al. and Bruinsma et al.. Foroohar and Bruinsma used two-dimensional and three-dimensional CT-scans for the review of proximal humerus fractures by their observers. On the one hand, this could imply that (our) surgeons may not require additional imaging techniques, such as CT-scans, for their classification of fractures. They may be highly capable in reviewing radiographs and picking up relevant details and clues in the radiographs. In addition, our proximal humerus fractures were relatively complex fractures due to the specific trauma mechanism while the fractures used in previous studies were not caused by high energy or velocity trauma. On the other hand, the fact that multi-dimensional images provide a better view of injuries and fractures is widely accepted and was concluded in an agreement study by Brunner et al. Shrader et al. may provide an argument for the documented consistency in interobserver agreement between the conservative and modern imaging modalities. They argued that the problem in understanding complex proximal humerus fractures is not the classification system themselves but rather than the use of modern imaging techniques to reveal the fracture patterns and anatomic changes.

As mentioned earlier in the introduction and literature review, the use of current classification systems remains a question of debate[28-30,42-47]. Given the eight categories of agreement as interpreted by Landis and Koch, our findings can only highlight the fact that the level of interobserver agreement for proximal as well as midshaft gunshot humerus fractures is low[32]. Although the AO/OTA classification provides a detailed description for many types of fractures, it demonstrated to result in only slight agreement in case of the radiological findings of the gunshot fractures. We found that the classification was the most frequently skipped question in our survey, with a compliance rate as low as 38% for some cases of proximal humerus fractures, while all other questions were answered with response rate of at least 94%. Together with the finding from literature that there is no gold standard for the classification of comminuted upper fractures caused by gunshots, this result may suggest that surgeons tend not to use the AO classification due to its limited usefulness in fractures caused by gunshot trauma.

Given the complexity of high-velocity gunshot trauma compared to the average complex fracture due to for example a bending force, the AO/OTA system may require further development to host this special type of fracture. An Australian research group compared the AO classification to the Neer classification and found better agreement of the latter among their three observers (moderate versus fair)[57]. They attempted to improve AO/OTA interobserver agreement by decreasing the number of options, but the outcomes did not improve. Despite the fact that modern imaging techniques have shown controversial effects in terms of interobserver reliability so far, Robinson et al. argued that the current classification systems should be revisited to incorporate three-dimensional reconstructions now available in the majority of institutions worldwide[45]. This may be advantageous for upper extremity specialists, who demonstrated the best interobserver and intraobserver agreement for classification in this study and who were shown to improve further by reviewing three-dimensional reconstructions as reported by Foroohar et al[29].

Junior registrars and trauma specialists reported the lowest agreement with kappa values of 0.15 and lower. It is interesting to observe that junior registrars at the one end of the spectrum are the least trained group with less than two years of experience while the trauma specialists at the other end are the most experienced surgeons who finished their specialist training years back. Junior registrars may not have had sufficient training yet whereas the trauma specialists may not be familiar with the AO classification (anymore), at least not as much as the senior registrars who are still in training and the upper extremity specialists who may have more exposure to classification systems in their daily clinical practice. These results may indicate that the two groups require additional training by for example senior registrars or upper extremity specialists. From another point of view however, this finding could also further confirm the hypothesis that fracture classification has limited clinical relevance. It was not found to be reliable even in the most experienced hands of trauma and upper extremity specialists.

Treatment

Overall interobserver reliability of agreement on treatment was lower ('slight') than the overall interobserver reliability on classification. Only trauma specialists achieved fair agreement with a significant difference compared to senior registrars and upper extremity specialists. Observer experience and the type of practice did not affect the interobserver reliability for management. It could mean that trauma specialists, more than other groups, are more focussed on management than on classification, possibly due to the acute emergency care setting in which they work. In terms of local relevance of these findings, this finding may suggest that the observers and their colleagues may need to open a discussion on their daily and best practices, opinions and experiences.

From a scientific point of view, these findings are not surprising and in fact correspond to the results of previous interobserver studies such as those by Foroohar and Bruinsma[28,29]. No interobserver reliability or agreement studies on diaphyseal humerus fractures were available for comparison. The finding that trauma surgeons demonstrated low agreement on fracture classification but were best in agreeing on the treatment raises the questions to whether classification is relevant for the eventual choice of management. Based on our results and the findings from literature regarding interobserver agreement and reliability of classification systems, we estimate this relevance as low. The low agreement on preferred treatment further emphasizes the need for research and development of guidelines on the management of humerus fractures expressed in the introduction and literature review.

Intraobserver agreement
Overall intraobserver reliability was fair for classification and moderate for treatment. The highest intraobserver reliability as indicated by mean and median kappa was achieved by the upper extremity specialists: moderate and close to substantial agreement for classification. This corresponds with the relatively good results in interobserver reliability as discussed before and supports the hypotheses that upper extremity specialists are best trained in the use of classification systems. Different from trauma specialists, upper extremity specialists may in general have more time for the evaluation of imaging, classification of injuries and surgical planning.

For treatment, trauma specialists had the best agreement (close to substantial), significantly different from the other groups, followed by upper extremity specialists. We hypothesise that trauma specialists may have scored best due to their skill of fast decision-making that could have worked in their advantage during the observer sessions in which there was only limited time to review X-rays and decide on treatment. No significant difference between type of fracture, type of practice and years of independent practice were found. This may suggest that the greatest challenge is not observer-related, but is rather associated with the characteristics and injury pattern of the fracture.

Secondary aims
Observers had moderate overall agreement on debridement of the wound and removal of the bullet and close to poor agreement for the use of temporary external fixators. Due to the dichotomy in answer options, this finding indicates that only a minority of observers would decide to use an external fixator. The best agreement was achieved for the removal of the bullet in cases of proximal humerus fractures. It appears that removal is common practice among observers, even though no consensus about whether or not to remove the bullet was found in literature.

For both midshaft and proximal fractures, vascular injury was the most influential factor as reported by more than half of the observers. Bilateral fractures and other injuries are also important in both types of fractures, as indicated by 14 to 44% of the observers. Hand dominance, neurological injury and employment status were identified as influential factors by less than one tenth of observers. For midshaft fractures in particular, other factors than the radiological findings were reported to influence the choice of treatment. Employment status was reported as an influencing factor by one tenth of observers. For proximal fractures, observers reported that additional information was not as influential for the choice of treatment. This may be due to a higher complexity of the fractures and less variety in treatment options. In a previous study on influencing factors on operative treatment for proximal humeral fractures, Hageman et al. found that older age was associated with a higher chance of conservative management compared to radiographs alone[30]. We did not find that sex influenced decision-making, which was similar to Hageman et al. who reported this variable to be used by less than 10% of the 238 surgeons. The percentage of surgeons that used hand dominance in their rationale was 4.7% in our study compared to 8.9% by Hageman et al. Overall, they concluded that clinical information did not lead to an increase in observer agreement[30].

Demographic patient-related factors were thus found to be of low influence on surgeon decision-making while injury-related factors tend to determine treatment to a significantly greater extent. Although we were unable to quantify the exact influence on a surgeon's decision, these findings are clinically relevant since they confirm our hypotheses that other variables than injury characteristics on images are part of surgical decision-making. Regardless of the clinical scenario, we found fair interobserver agreement with respect to debridement and removal of the bullet. Close to poor agreement was found for the question as to whether or not to use an external fixator. Unfortunately, there is no evidence concerning these questions available for reference.

Limitations

The findings presented and discussed should be interpreted against a number of limitations. Firstly, half of the observers were surgeons still in training or surgeons who had less than five years of clinical experience. The outcomes of this study may thus change with different observer demographics. Second, observers were not informed about the classification system or treatment protocols before the start of the first session as we aimed to gain insight in their decision-making based on practice and experience. Third, the quality of radiographs presented in the Powerpoint is likely to be different from how a surgeon normally reviews the radiological features of a case. Half of the observers indicated that the available information was insufficient. In the fourth place, we were unable to use predictive analytics such as logistic regression to statistically assess the relation between independent variables on the choice of treatment. Observers were insufficiently instructed on how to use the answer sheet to express their preferences and decisions.

Conclusions

Our comprehensive literature review highlights the lack of evidence-based guidelines for treating gunshot-related humerus fractures. This study aimed to define the intra- and interobserver reliability of classification and treatment for gunshot-related humerus fractures in an armed violence endemic area. We hypothesised that interobserver reliability is low for the AO classification and high for treatment; that there is no difference in interobserver reliability between different types of surgeons and that intraobserver reliability is high.

Overall interobserver agreement on preferred treatment demonstrated to be lower (slight) than overall interobserver agreement on classification. Interobserver agreement for classification was highest among senior registrars and upper extremity specialists while trauma specialists agreed best on the treatment. Average agreement was slight, which emphasises the consistently low interobserver agreement for the classification and treatment of proximal humerus fractures found in literature. Overall intraobserver reliability was fair for classification and moderate for treatment.
The highest intraobserver reliability was achieved by the upper extremity specialists, corresponding to good interobserver reliability which may mean upper extremity specialists are best trained in the use of the AO classification systems. Since experienced

and specialized trauma surgeons in particular demonstrate low interobserver agreement on classification with significantly higher agreement on treatment, we may conclude that the clinical relevance of classification systems for gunshot-related humerus fractures is very limited. Agreement on debridement and removal of the bullet was moderate, while agreement on the use of an external fixator was close to poor. Injury-related factors such as vascular injury and additional fractures or injuries were found to significantly influence surgical decision making while patient factors such as sex and hand dominance were not associated with the choice of management.

Strengths of this study include the novel research question, comprehensive literature review, large number of observers, the addition of patient and injury-related factors in the study of surgeon decision-making and the experience of our practicing registrars and trauma and upper extremity specialists in an area known for its high gunshot trauma burden. In future research, we plan to increase the number of observers and to provide the observers with better instructions on how to rate the classification and outcomes after reviewing additional patient information. Future studies should compare the preferred treatment to the actual treatment received and include multi-dimensional imaging techniques. The most urgent recommendation is to motivate orthopaedic trauma and upper extremity surgeons worldwide to conduct similar studies in order to compare our results with international perspectives and to obtain better insights into the rationale behind classification and treatment[49,50]. The consistent slight to fair levels of agreement from international studies and studies from different continents call for the development of guidelines and protocols, thereby allowing the treating surgeons to treat their patients with gunshot-related humerus fractures according to modern evidence-based medicine.

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Appendix

1. Informed consent form

<u>Form I: Informed Consent Observers</u>

Project information
Title: Intra- and interobserver reliability regarding gunshot humerus fractures
Department: Orthopaedic Surgery, Groote Schuur Hospital, University of Cape Town, South Africa
HREC: Approval number 059/2017, prof. Blockman (marc.blockman@uct.ac.za)

Synopsis
Conduct of study
Sociodemographic and educational background of participants is not relevant to this study since we will only use patients' radiographs without patient demographics or clinical information. We will however include 'fake' scenarios our survey to evaluate whether for example comorbidities or hand dominance influence clinical and surgical decision-making.

Purpose
The purpose of this study is to assess the inter- and intraobserver agreement in the classification and treatment of gunshot injuries leading to humerus fractures in a gunshot trauma endemic area. No consensus can be found in literature regarding the classification and management of gunshot injuries to the upper extremity. There is no protocol or guideline on how to treat such injuries. The study will provide insights into clinical decision-making and the determinants, and may give us directions for a prospective study in which we compare different choices of management in a controlled setting. This protocol is thus a solid first step in the development of evidence-based practice for upper extremity gunshot humerus and that is why our study has important benefits for (future) patients.

Research question
What is the level of inter- and intraobserver agreement and reliability in the injury classification and management in patients with humerus gunshot fractures evaluated by an expert panel?

Study design and criteria
This is an agreement and reliability study performed with an expert panel of 32 observers who will answer questions on various images of a 32 cases with humerus fractures (16 proximal, 16 mid-shaft) due to gunshot injuries. Patients with proximal humerus fractures as well as patients with humerus shaft fractures due to gunshot injuries, for which high-quality radiographs are available, are eligible for inclusion as a case. Distal fractures and other upper extremity fractures are excluded.

Recruitment

Observers: The panel will consist of 8 junior registrars, 8 senior registrars, 8 orthopaedic trauma surgeons and 8 specialized upper extremity surgeons with various degrees of experience (years of training or independent practice). Participants will be invited by principal investigator prof. dr. Roche.

Cases: We will construct a list of consecutive patients with humerus fractures due to gunshot trauma who presented at the Trauma Unit and were thus included in the electronic Trauma Health Record database (eTHR). We aim to start including from July 2014 when the eTHR was in good use until we have included our sample size of 32. Inclusion of consecutive patients from this database reduces selection bios when for example compared to the theatre database.

Potential harms
There is no probability of any kind of harm since we will only collect 32 X-rays without other patient information. Privacy is protected by deleting confidential data from the X-rays and data will not be stored on laptops or online data systems. Risks are thereby minimised and safety is protected. All patients have already been treated and the outcomes of this study will thus not have impact on their treatment or follow-up management.

Benefits
The study will provide insights into clinical decision-making and the determinants, and may give us directions for a prospective study in which we compare different choices of management in a controlled setting. This protocol is thus a solid first step in the development of evidence-based practice for upper extremity gunshot humerus and that is why our study involves important benefits for (future) patients.

Compensation
In this observational reliability study, we retrospectively collect data and there are no research-related costs or inconvenience for cases included. There is no compensation or insurance required.
Observers will not be rewarded be involved in the design, conduct and analysis of this study. They participate in the study and will be acknowledged, but they cannot be authors in order to prevent bias.

Informed consent
Consent was obtained for all patients for imaging and treatment. The reviewers will receive a clear description of the study and will be asked for informed consent; data will only be used after informed consent has been given.

Ethics
This study does not have any morally controversial aspects. There are no restrictions on publication.

Aim
The aim of this intra- and interobserver reliability study is to obtain more insight into clinical decision-making among different surgeons in patients with gunshot fractures of

the humerus. The survey consists of 32 X-rays and four standard questions for each X-ray. There is no right or wrong answer to the questions asked.

Confidentiality
The researcher will use the answers provided by you for the purposes of this study and for scientific merit. The information will be stored both on computer. To protect your privacy, the information will be labelled in a way that will not identify you. The researcher will assign a code to you and your information and samples will be known only by that code. If the results of this study are published, your identity is kept confidential. The information collected will only be available to the researchers mentioned below and will not be sent to other people or third parties. By signing this form, you are permitting this use of the study information in this way.

Use of data
Data will only be used after informed consent has been given. We will ask you to complete a survey twice with an interval of two weeks. The information can only be used if both surveys are completed. If you decide to leave the study at any time, the researcher may still use your information collected up to that point.

Reimbursement
Patients will not be reimbursed for participation in the study. The only incentives for observers to participate will be the group acknowledgement in the manuscript, scientific curiosity and camaraderie.

Contact
For more information or questions about this study, please connect with Esmee Engelmann.

Authorization
I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study.

Observer name ______________________

Date and Place ______________________

Signature

____

Corresponding researcher: Esmee Engelmann (e.w.engelmann@amc.uva.nl)
Supervisor: Prof. S. Roche (stephen.roche@uct.ac.za)

2. Questionnaire and answer forms

INSTRUCTIONS: Please answer the questions below for each and every case (23 in total), based on the multiple view X-rays presented. Answers should be noted on the answer sheet provided. Please make sure you note at least thirteen answers (Q1-Q14) for each case, as answers can not be used if the survey is not filled in completely. Many thanks in advance.

*** Classification**
Q1: Classify the fracture according to the AO rules and options.

*** Treatment**

Q2: Debridement	yes/no
Q3: Remove bullet	yes/no
Q4: Use of temporary external fixator	yes/no
Q5: Treatment of choice	
	–Conservative (plaster/splint) –Intramedullary nail –ORIF plating: compression/neutralizing a) locking screw b) non locking screw - ORIF plating: bridge plating a) locking screw b) non locking screw –External fixator

*** Clinical scenario**
Would your treatment change for each of these clinical scenarios? If yes, please note how?

Q6: Male or female?	Yes/no
Q7: Employed or unemployed?	Yes/no
Q8: This is the dominant hand?	Yes/no
Q9: In case of bilateral upper extremity fractures?	Yes/no
Q10: In case of vascular damage?	Yes/no
Q11:In case of neurological injury?	Yes/no
Q12: In case of other additional fractures?	Yes/no

*** Quality**

Q13: Are the X-rays good enough?	Yes/no
Q14: Any other comments?	

II Example of answer sheet

PLEASE MAKE SURE TO USE YOUR OWN OBSERVER NUMBER
Observer number (*allocated by researcher):* ________________________________

Demographics *(cross or write down answer:*
Sex: ○ Male
○ Female

Age: ______________________________
Hospital: ______________________________
Type of surgeon:
- ○ Junior Registrar (<3 yrs of training)
- ○ Senior Registrar (>3 yrs of training)
- ○ Orthopaedic Trauma Specialist
- ○ Upper Extremity Specialist
- ○ Other, ______________________

Years in independent practice:
- ○ 0-5
- ○ 6-10
- ○ 11-20
- ○ 21-30

Supervising trainees in theatre:
- ○ Yes
- ○ No

Cases

<u>Case 1</u>

1: Classification AO/OTA

○ 12A1	○ 12A2	○ 12A3
○ 12B1	○ 12B2	○ 12B3
○ 12C1	○ 12C2	○ 12C3

2: Debridement ○ Yes ○ No
3: Remove bullet ○ Yes ○ No
4: Temporary ex-fix ○ Yes ○ No
5: Treatment
- ○ Conservative
- ○ Intramedullary nail
- ○ ORIF plating; compression/neutralizing plate
  - ○ Locking screw
  - ○ Non-locking screw
- ○ ORIF plating; bridge plate
  - ○ Locking screw
  - ○ Non-locking screw
- ○ External fixator

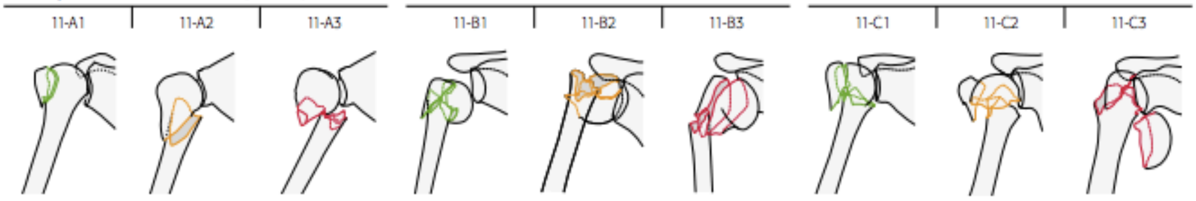
	Change	*Explain how*
6: Male or female	○ Yes ○ No	______________________
7: Employed or unempl.	○ Yes ○ No	______________________
8: Dominant hand	○ Yes ○ No	______________________
9: Bilateral UE #	○ Yes ○ No	______________________
10: Vascular damage	○ Yes ○ No	______________________
11: Neurological injury	○ Yes ○ No	______________________
12: Other additional #	○ Yes ○ No	______________________

13: Sufficient quality ○ Yes ○ No
14: Comments ____
____

3. AO/OTA classification

1 Humerus

11 proximal (types according to topography and extent of bone lesion)

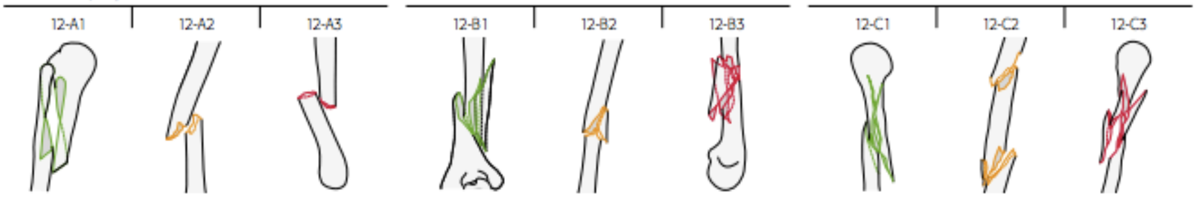


11-A extraarticular unifocal fracture
11-A1 tuberosity
11-A2 impacted metaphyseal
11-A3 nonimpacted metaphyseal

11-B extraarticular bifocal fracture
11-B1 with metaphyseal impaction
11-B2 without metaphyseal impaction
11-B3 with glenohumeral dislocation

11-C articular fracture
11-C1 with slight displacement
11-C2 impacted with marked displacement
11-C3 dislocated

12 diaphyseal

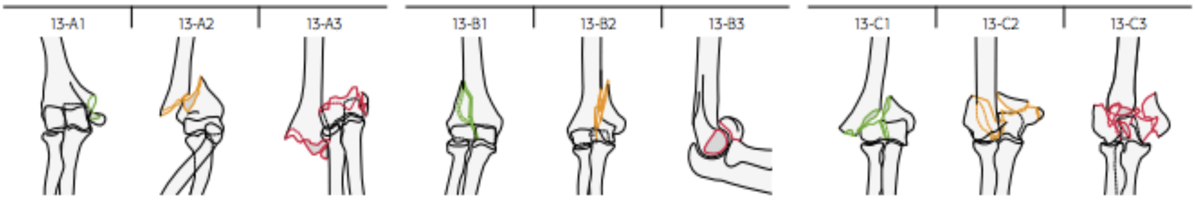


12-A simple fracture
12-A1 spiral
12-A2 oblique (≥ 30°)
12-A3 transverse (< 30°)

12-B wedge fracture
12-B1 spiral wedge
12-B2 bending wedge
12-B3 fragmented wedge

12-C complex fracture
12-C1 spiral
12-C2 segmental
12-C3 irregular

13 distal



13-A extraarticular fracture
13-A1 apophyseal avulsion
13-A2 metaphyseal simple
13-A3 metaphyseal multifragmentary

13-B partial articular fracture
13-B1 sagittal lateral condyle
13-B2 sagittal medial condyle
13-B3 coronal

13-C complete articular fracture
13-C1 articular simple, metaphyseal simple
13-C2 articular simple, metaphyseal multifragmentary
13-C3 articular multifragmentary

4. Kappa interpretation by Landis and Koch[32]

Kappa value	**Agreement**
-1.00	Total disagreement
0	None*
0.01-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-0.99	Almost perfect
1.00	Perfect agreement

*Chance agreement. Although kappa values ranging 0 to -1 are possible, they rarely occur since it represents an agreement less than that would occur by random chance.

5. Intra-rater reliability per observer

Observers	k class	SE class	k treatm	SE treatm
3	0.338	0.113	0.171	0.17
5	0.41	0.133	0.165	0.196
6	0.433	0.152	0.689	0.133
7	0.593	0.115	-0.039	0.033
8	0.033	0.054	0.096	0.147
10	0.398	0.074	0.219	0.15
11	0.265	0.113	0.797	0.106
12	0.22	0.089	0.306	0.201
13	0.661	0.148	0.331	0.124
14	0.564	0.123	0.57	0.158
15	0.353	0.117	0.594	0.147
16	0.386	0.118	0.783	0.115
17	0.561	0.104	0.154	0.141
19	0.42	0.129	0.66	0.167
21	0.545	0.16	0.113	0.166
22	0.25	0.096	0.385	0.166
23	0.86	0.133	0.723	0.118
24	0.689	0.137	1	0
25	0.206	0.096	0.272	0.154
26	0.664	0.105	0.602	0.198
28	0.021	0.063	0.078	0.136
29	0.113	0.116	0.284	0.14
30	0.428	0.12	0.391	0.148
31	0.395	0.134	0.391	0.176
32	0.318	0.138	0.403	0.166
33	0.146	0.105	0.711	0.13
34	0.308	0.105	0.544	0.144

k = Cohen's kappa, SE = standard error.

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 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 February 2017

HREC REF: 059/2017

A/Prof Steve Roche
Orthopaedics
H49, OMB

Dear A/Prof Roche

PROJECT TITLE: PERSPECTIVES ON THE MANAGEMENT OF HUMERUS FRACTURES DUE TO GUNSHOT TRAUMA: AN INTER- AND INTRA-OBSERVER AGREEMENT AND RELIABILITY STUDY (Masters-candidate-E Engelmann)

Thank you for your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study subject to adding the HREC contact details to the informed consent document.

Approval is granted for one year until the 28th February 2018.

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.

The HREC acknowledge that the student, Esmee Engelmann will also be involved in this study.

Yours sincerely

Signed by candidate

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 Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI),and Declaration of Helsinki (2013) guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Compensation
In this observational reliability study, we retrospectively collect data and there are no research-related costs or inconvenience for cases included. There is no compensation or insurance required. Observers will not be rewarded be involved in the design, conduct and analysis of this study. They participate in the study and will be acknowledged, but they cannot be authors in order to prevent bias.

Informed consent
Consent was obtained for all patients for imaging and treatment. The reviewers will receive a clear description of the study and will be asked for informed consent; data will only be used after informed consent has been given.

Ethics
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Aim
The aim of this intra- and interobserver reliability study is to obtain more insight into clinical decision-making among different surgeons in patients with gunshot fractures of the humerus. The survey consists of 32 X-rays and four standard questions for each X-ray. There is no right or wrong answer to the questions asked.

Confidentiality
The researcher will use the answers provided by you for the purposes of this study and for scientific merit. The information will be stored both on computer. To protect your privacy, the information will be labelled in a way that will not identify you. The researcher will assign a code to you and your information and samples will be known only by that code. If the results of this study are published, your identity is kept confidential. The information collected will only be available to the researchers mentioned below and will not be sent to other people or third parties. By signing this form, you are permitting this use of the study information in this way.

Use of data
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Authorization
I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study.

Observer name N Wagner

Date and Place 17/7/17

Signature

Signed by candidate

Corresponding researcher: Esmee Engelmann (e.w.engelmann@amc.uva.nl)
Supervisor: Prof. S. Roche (stephen.roche@uct.ac.za)

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Observer name

Date and Place 17 | 1

Signature Signed by candidate

Corresponding researcher: Esmee Engelmann (e.w.engelmann@amc.uva.nl)
Supervisor: Prof. S. Roche (stephen.roche@uct.ac.za)

Compensation
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Observer name S. MAQUNGO

Date and Place CAPE TOWN 2017/2/27

Signature Signed by candidate

Corresponding researcher: Esmee Engelmann (e.w.engelmann@amc.uva.nl)
Supervisor: Prof. S. Roche (stephen.roche@uct.ac.za)

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Observer name BRIAN BERNSTEIN

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Date and Place 16/2/2017

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Reimbursement
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Contact

For more information or questions about this study, please connect with Esmee Engelmann.

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I have read and understand this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal fault of anyone who is involved in this study.

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Date and Place __/______

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Supervisor: Prof. S. Roche (stephen.roche@uct.ac.za)

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In this observational reliability study, we retrospectively collect data and there are no research-related costs or inconvenience for cases included. There is no compensation or insurance required. Observers will not be rewarded be involved in the design, conduct and analysis of this study. They participate in the study and will be acknowledged, but they cannot be authors in order to prevent bias.

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