Title page

Title: The effect of Mulligan's Mobilization with Movement following Total Knee Arthroplasty: Protocol of a Single-Blind Randomized Controlled Trial.

Authors:
Dr. Najla F. Alsiri[1], MSc, PhD. Email: dr.alsiri@outlook.com
Dr. Meshal A. Alhadhoud[2], MBBCh. SB-Orth, MBA. Email: Maalhadhoud@gmail.com
Dr. Ali Al-Mukaimi[1], MBBCh. Email: Mukaimi@hotmail.com
Prof. Shea Palmer[3], PhD. Email: Shea.pamer@uwe.ac.uk
[1] Al-Razi Orthopedics and Rehabilitation Hospital, Kuwait.
[2] Al-Adan Hospital, Kuwait.
[3] Department of Allied Health Professions, Faculty of Health and Applied Sciences, University of the West of England, Bristol, UK.

Corresponding author: Dr. Najla F. Alsiri, Al-Razi Orthopedics and Rehabilitation Hospital, Shuwaikh, Kuwait. Email: dr.alsiri@outlook.com.
Tel: 00965-66820032

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Abstract:

Background: Mulligan's Mobilization with Movement aims to enhance the kinematics of the joint. Kinematic impairment of the knee joint is significant following Total knee Arthroplasty, which could be managed with Mulligan's Mobilization with Movement. This manuscript describes the study protocol for a single-blind randomized controlled trial investigating the effectiveness of Mulligan's Mobilization with Movement following Total Knee Arthroplasty.

Methods: A single-blind randomized controlled trial design will be employed to compare two groups: an intervention and control group. Each group will attend a standard post-operative rehabilitation program. The intervention group will additionally receive articular mobilization using a Mulligan's Mobilization with Movement approach. A blinded examiner will assess participants at four points: pre-operation, three weeks post-operation (when the intervention starts), six weeks post-operation (when the intervention ends), and at six months as a long-term follow-up. The two groups will be compared on the basis of knee range of motion (standard goniometry), knee joint pain (Visual Analogue Scales), walking speed using (15-meter walk test), functional mobility (timed up and go test), and participation (Western Ontario and McMaster Universities Osteoarthritis Index questionnaire). A blinded examiner will measure knee joint alignment using a computed tomography scanogram pre-operatively and at three months post operation. Mixed model ANOVA will be used to identify any group differences. Ethical approval has been secured from the ethical committee of the X Ministry of Health, and the trial is registered in the ISRCTN registry (ref:13028992).

Discussion: The study findings could inform the optimization of post-operative rehabilitation of patients following TKA.

Key words: Total Knee Arthroplasty, Rehabilitation, Mobilization with Movement.

1. Introduction:

Knee osteoarthritis (OA) is a chronic progressive degenerative disease of the intra-articular cartilage (Giwnewer et al., 2016; Hussain et al., 2016). OA is the most common arthritis of the knee due to its multi-etiological factors including advancing age, being a female, being overweight, repetitive overuse, genetics and occupational factors (Giwnewer et al., 2016). The intra-articular cartilage acts as a joint protector by cushioning the bone endings of the knee joint during movement (Giwnewer et al., 2016; Hussain et al., 2016; Wang et al., 2016). The degenerative changes in OA lead to thinning and loosening of the intra-articular cartilage, sclerosis of the subchondral bone, and cyst and osteophytes formation (Wang et al., 2016). These intra-articular degenerative changes lead to pain, swelling, inflammation and joint stiffness (Giwnewer et al., 2016). The severe symptomatic features of OA impact upon walking ability and performing the daily activities (Cross et al., 2014; Na, Piva and Buchanan, 2018). Globally, knee OA has been ranked the eleventh highest cause of disability (Cross et al., 2014; Kee et al., 2017).

Total knee arthroplasty (TKA) is a successful surgical procedure for the advanced stage of OA (Hussain et al., 2016; Quinn et al., 2018). In 2012, more than 670,000 TKAs were performed in the United States at an estimated cost of 36.1 billion dollars, and the number of TKAs is expected to increase by 137% in 2030 (Kurtz et al., 2007; Skou et al., 2015). TKA is considered after the failure of conservative interventions such as non-steroidal anti-inflammatory drugs, weight loss and life-style modification, physical therapy, orthotic devices and intra-articular injections (Giwnewer et al., 2016; Hussain et al., 2016; Abbasi, 2017; Xing et al., 2017; Quinn et al., 2018). TKA aims to reconstruct the knee joint by resurfacing the damaged intra-articular parts using metal and plastic artificial prostheses (Giwnewer et al., 2016; Quinn et al., 2018; Varacallo, Luo and Johnson, 2020).

However, normal knee mobility is not restored with TKA. Six months post-TKA, joint function, strength and activity levels return to the pre-operative level, but normal knee flexion does not (Lowe et al., 2007; Bade, Kohrt and Stevens-Lapsley, 2010; Henderson, Wallis and Snowdon, 2018). The highest reported mean knee flexion in a systematic review and meta-analysis was 108^0 recorded at 12 months post-TKA (Mockford et al., 2008). Higher knee flexion of 120^0 has been reported as required to efficiently perform essential tasks including kneeling, squatting, cross-legged sitting, stair climbing, stepping into a bathtub, and professional and recreational activities (Walker and Garg, 1991; Rowe et al., 2000; Li et al., 2004). Limited knee flexion following TKA is related to preoperative, intraoperative and postoperative factors (Li et al., 2004). Changes in knee kinematics is one of the main factors that affects the ability to restore knee mobility, where kinematics reflect joint angular changes and movement sequences in respect to time (Hall, 1999). Attaining higher knee flexion requires synchronized accessory intra-articular translation and rotation. Greater internal tibial rotation with posterior femoral condyle translation are required throughout knee flexion to maximize knee flexion (Li et al., 2004). However, TKA alters normal knee kinematics, where paradoxical femoral condyle anterior movement is found (Stiehl et al., 1995; Zelle, Van der Zanden and De Waal Malefijt, 2009). Reduced posterior femoral translation causes impingement of the posterior edge of the tibial component, which limits knee flexion (Andriacchi and Galante, 1988; Walker and Garg, 1991; Hartford et al., 2001; Li et al., 2005). An in-vitro robotic study explored TKA kinematics at lower and higher angles (Li et al., 2004). At 90^0 flexion, the posterior translation of the lateral femoral condyle was significantly lower in TKA: 6.7 ± 6.2 mm, compared to the intact knee: 13.8 ± 7.0 mm (Li et al., 2004). At 90^0 flexion, the posterior translation of the medial femoral condyle was found to be significantly lower in TKA: 2.6 ± 5.3 mm, compared to the intact knee: 9.1 ± 6.8 mm (Li et al., 2004). Significant reductions in tibial internal rotation were also found in TKA at 30^0 and 60^0 of flexion (Li et al., 2004). At

higher angles of 90^0 to 150^0 of flexion, significantly lower lateral femoral condyle posterior translation was revealed (Li et al., 2004).

Post-operative rehabilitation is essential for TKA to reduce pain and improve joint function and overall activity (Naylor et al., 2006). The effectiveness of post-operative rehabilitation regimes for TKA have been studied, including strengthening programs, neuromuscular electrical nerve stimulation, and continuous passive motion (Beaupré et al., 2001; Minns Lowe et al., 2007; Artz et al., 2015; Florez-García et al., 2017; Henderson, Wallis and Snowdon, 2018; Yue et al., 2018; Yang et al., 2019). However, none of the explored regimes have examined the benefit of articular mobilization. More importantly, the standard rehabilitation programs do not maximize knee flexion in TKA (Lowe et al., 2007; Mockford et al., 2008). A systematic review and meta-analysis concluded that TKA rehabilitation programs need to be better designed and target specific limitations (Lowe et al., 2007). The effectiveness of articular mobilization techniques has been demonstrated to increase motion and reduce pain in patients suffering from neck pain, shoulder impingement syndrome, adhesive capsulitis, and ankle sprain (Hoving et al., 2002; Collins, Teys and Vicenzino, 2004; Senbursa, Baltaci and Atay, 2007; Vicenzino, Paungmali and Teys, 2007; Yang et al., 2007; Do Moon et al., 2015). Yet, the effectiveness of articular mobilization techniques, including Mulligan's Mobilization With Movement (MWM), has not examined in relation to TKA. MWM is a widely used class of joint mobilization algorithm, where a manual force is used to sustain translational or rotational articular glides to facilitate active physiological movement (Mulligan, 1999; Vicenzino, Paungmali and Pamela, 2007). TKA significantly reduces the knee accessory kinematics that impact knee flexion, as previously discussed (Stiehl et al., 1995; Li et al., 2004; Zelle, Van der Zanden and De Waal Malefijt, 2009). The potential therapeutic effect from MWM of improving joint kinematics by enhancing both accessory and physiological movements could be utilized to maximize knee flexion following TKA;

ultimately restoring the functional capacity to perform various daily, professional and recreational activities. The existing rehabilitation programs for TKA focus purely on knee flexion and extension, while the knee joint permits six degrees of movement (Robertson et al., 2003; Amis, 2017; Vaienti et al., 2017). MWM may be of benefit as an adjunct to other rehabilitation approaches and contribute toward enhanced rehabilitation. Therefore, the study aims to examine the effectiveness of MWM following TKA using a randomized controlled trial design.

2. Methods:

2.1 Study design:

A single-blind randomized controlled trial design will be employed, randomly allocating TKA patients into two groups: Control Group (CG) and MWM Group (MWMG). An online research randomizer will be used to inform allocation; v4.0 (http://www.randomizer.org, Geoffrey C. Urbaniak and Scott Plous). With simple randomization, the randomizer will generate 80 sets of numbers in a random order from 1-80. The random list will be used to prepare sequentially numbered envelopes with relevant allocation; a patient with odd number will be assigned to the CG and a patient with an even number will be assigned to the MWM group, which will permit equal group sizes.

The CG will attend a conventional post-operative rehabilitation program without any form of articular mobilization techniques. The MWMG will receive the Knee MWM technique in addition to the conventional post-operative rehabilitation program. Patients in each group will receive individual one to one rehabilitation. The study has been approved by the Ethical Committee of X Ministry of Health (ref:698/2018) and registered on the ISRCTN registry (ref:13028992). Informed consent will be obtained and patients' rights will be maintained according to the Declaration of Helsinki (The World Medical Association, 2008).

The examiners will be blinded from group allocations to avoid expectation bias. Due to the nature of the intervention, it will not be possible to blind the patients. The aim of the study will be explained to the patients, and they will be told that if they have been assigned to the MWMG they will receive six sessions of knee mobilization, which could provide benefit to their operated knee.

2.2 Sample size calculation:

Knee flexion range of motion measured at week six post-TKA is considered the primary outcome measure. A study by Jakobsen et al., was used to inform the sample size calculation, where the smallest difference for knee goniometry post-TKA was identified as 10^0 between raters (Jakobsen et al., 2020). Differences smaller than 10^0 could therefore be considered as measurement error. Nineteen patients were included, and knee flexion was measured at a mean of 50 ± 15.3 days post-operation (Jakobsen et al., 2020), similar to the six week time-point in the current study. The mean passive knee flexion measured by an experienced therapist on the first round of testing was $110.0^0 \pm 12.6^0$, which can be considered a fair estimate of knee flexion six weeks post-operation in a control group (Jakobsen et al., 2020). The following figures were therefore used for calculation: CG = $110.0^0 \pm 12.6^0$ and MWMG = $120.0^0 \pm 12.6^0$; assuming a minimum 10^0 increase in flexion and a similar standard deviation. The resultant effect size of 0.79, with a two tailed hypothesis, means a calculated sample size of at least 35 participants per group at (α) 0.05 and a power (1- ß) of 90%. 40 participants per group will be recruited to account for attrition.

2.3 Inclusion and exclusion criteria:

Patients will be recruited from X Hospital, which is the main specialized orthopedic hospital in X. The diagnosis of knee OA will be confirmed by an orthopedic surgeon according to the criteria of the American College of Rheumatology (Christopher et al., 2005). Patients scheduled for TKA due to symptoms of OA will be included. The inclusion criteria include

183 women in the age range of 40-80 years. X Hospital is a large multi-building institution, where
184 female patients have their orthopedic wards in a separate building with a designated
185 physiotherapy department and staff. Managing one project between two different buildings is
186 not practical, and as women are at higher risk of knee OA, it was decided to conduct this study
187 in the female facilities.

188 The exclusion criteria include secondary OA, inflammatory joint disease, peripheral
189 vascular disease or severe cardiac disease, and inability to comprehend Arabic. Patients who
190 are scheduled for bilateral TKA, have previous fractures in or adjacent to the knee joint or
191 neurological deficits will be excluded.

192 ***2.4 Conventional post-operative rehabilitation program (Hoffmann et al., 2014):***

193 Each group will attend a conventional post-operative rehabilitation program (the
194 hospital's standard protocol) which starts from day two post-operation for a standardized
195 duration of three months. For one week, post-operative patients will attend an individualized
196 daily rehabilitation during their stay at the hospital. After discharge, the rehabilitation will be
197 twice per week at the physiotherapy outpatient department and conducted by specialized
198 physiotherapists, including range of motion and strengthening exercises, such as knee
199 flexion/extension, short/long arcs, straight leg raising, circulatory exercises and open/closed
200 chain kinematic exercises. The program will include gait and stair training and cycling. The
201 number of rehabilitation sessions and adherence to the intervention will be recorded. The
202 intervention intensity and progression criteria will be tailored according to each patient's needs,
203 aiming to reduce pain, improve range of motion and strength and enable the performance of
204 daily activities.

205 ***2.5 Knee Mobilization With Movement (Hoffmann et al., 2014):***

206 The MWMG will receive knee MWM from week three post-TKA; twice per week for
207 three weeks, thereby administering a total of six sessions at the physiotherapy outpatient

208 department. It has been decided to start the intervention at week three post-TKA to allow the
209 surgical incision to heal, because MWM requires the application of over-pressure at the end-
210 range. Before starting MWM, the physiotherapist will inspect the wound to ensure the incision
211 has healed. The intervention approach of MWM will target knee flexion following Mulligan's
212 guidelines (Mulligan, 1999; Vicenzino, Paungmali and Pamela, 2007). Two expert
213 physiotherapists who are trained in the Mulligan concept will determine the knee faulty
214 position to decide which mobilization technique to use for each patient individually. The
215 following MWM techniques can be used according to the patient's needs: medial glide, lateral
216 glide, medial rotation, lateral rotation, or anterio-posterior (Mulligan, 1999; Vicenzino,
217 Paungmali and Pamela, 2007). For all the techniques, the patient will be in a supine position
218 and a Mulligan belt (Mulligan Manual Therapy Concept ^{TM}) will be placed around the feet and
219 held by the patient, who will actively flex the knee during MWMs and apply over pressure at
220 the end of the range. For medial/lateral glide MWMs, the practitioner will medialy/lateraly
221 glide the tibia, for rotational MWMs, the practitioner will medially/laterally rotate the proximal
222 part of the leg, and for anterio-posterior MWMs, anterio-posterior glide on the tibia will be
223 applied (Mulligan, 1999; Paungmali and Pamela, 2007; Vicenzino, Hing, Hall and Mulligan,
224 2015). All glides will be performed during active knee flexion and sustained through the
225 movement from flexion and returning to the starting position. Each mobilization technique will
226 be performed for three sets of ten times (Mulligan, 1999; Paungmali and Pamela, 2007;
227 Vicenzino, Hing, Hall and Mulligan, 2015). The intervention for each patient can be modified
228 during the course where the physiotherapist will re-determine the optimal technique before
229 each session. Intervention details will be recorded on a customized sheet by the physiotherapist,
230 including the number of sessions, intervention adherence and the techniques used.

231 ***2.6 Outcome Assessment:***

The two groups will be examined at four time points: 1) pre-operative examination, one to three days before surgery, 2) three weeks post-operation (when the MWMG will start the MWM intervention), 3) six weeks post-operation (when the MWMG will have received six sessions of MWM), and 4) six months post-operation as a long-term follow-up. One blinded examiner who is a physiotherapist with 15 years' experience in orthopedic rehabilitation will examine the two groups using outcome measures reflecting impairment, activity and participation. Another blinded examiner, who is a consultant orthopedic surgeon, will measure knee mechanical alignment at two points: pre-operation and three months post-operation.

The examination at the four time points will include measures related to impairment, activity and participation, as recommended by the World Health Organization, using the International Classification of Functioning, Disability and Health (ICF) (World Health Organization, 2002). A designated sheet will be used to record patients' demographics and details, including age, height, weight, and medical history. In terms of impairment, knee range of motion, pain and mechanical alignment will be measured. Knee range of motion will be measured using a 12-cm hand-held universal goniometer, the lateral femoral epicondyle as the measurement center led by the lateral malleolus and the greater trochanter. The Goniometer is clinically applicable and shows the least measurement error in comparison with much more technically intensive methods of sequential magnetic resonance imaging (MRI) and two-dimensional motion analysis (Piriyaprasarth and Morris, 2007). To measure passive knee extension, in a supine position, the heel of the operated limb will be placed on a 12-cm diameter bolster. The contralateral limb will be fully extended, and the examiner will apply pressure to extend the knee. The knee will then be passively flexed, and the flexion measurement will be taken, where the examiner will apply pressure to flex the knee. Two measurements will be recorded, and the mean will be used for knee flexion and extension. The average intensity of knee pain over the last week will be measured using Visual Analogue Scales (VAS) during

both rest and movement. The VAS is a simple 10-cm length pain assessment tool, which is highly valid, reliable, and sensitive (Bijur, Silver and Gallagher, 2001; Lara-Munoz, 2004; Williamson and Hoggart, 2005). The second blinded examiner will measure the mechanical alignment of the lower limb, which is a measure of the hip-knee-ankle angle captured using a computed tomography scanogram. The mechanical alignment is sufficiently accurate compared to intra-operative measurement (Mohanlal and Jain, 2009). It is a line extended from the femoral head center to the ankle center and normally passes across the knee joint center, which should be restored to neutral with TKA (Mohanlal and Jain, 2009). This measure will determine the implant's proper alignment (Bellemans et al., 2002; Mohanlal and Jain, 2009).

Regarding the activity domain, walking speed and the timed up and go test will be introduced. The timed up and go test examines functional mobility, balance and risk of falling, which is an easy test, clinically applicable and does not require specialized tools (Mathias, Nayak and Isaacs, 1986; Podsiadlo and Richardson, 1991). The patient will be timed from rising from an approximately 46 cm height chair, walking at a comfortable speed for three meters, turning, and returning to the chair (Mathias, Nayak and Isaacs, 1986; Podsiadlo and Richardson, 1991). The floor will be labeled at three meters distances. The test will be performed once for familiarization. This test will be performed with footwear and using the patients' usual walking aid. The faster the time, the better the functional performance is. Additionally, gait speed will be measured along a 15-meter distance using a self-selected walking speed (Cheng et al., 2020). Both tests will be conducted twice and the mean will be recorded.

Regarding participation, the Arabic version of the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire (WOMAC) will be used which is highly valid, reliable and specific (Bellamy et al., 1988; Alghadir et al., 2016).

2.7 Data collection procedures:

Patients who are elected for TKA will be admitted one day pre-operation every Sunday, as an admission policy for the arthroplasty unit. Monday is the day of surgery. Every Sunday, the principal investigator (PI) will use the admission note and the patient files to recruit potential participants. If any exclusion criteria are noticed in the patient file, the patient will not be approached. However, if the file shows no exclusion criteria, the patients will be approached. The research's purpose, protocol, examination procedures and timing will be explained, and the inclusion and exclusion criteria will be checked. If the patient meets the eligibility criteria and agrees to take part in the study, they will be asked to read and sign the consent form. Then the patient will be randomly allocated by the PI to the MWMG or CG. The Consolidated Standards of Reporting Trials will be used (Figure 1) (Schulz, Altman and Moher, 2010). The PI will then contact the blinded examiner to examine the patient in the physiotherapy department. The height and weight will be measured, and then the demographic sheet, VASs and WOMAC questionnaire sheets will be filled in. Knee range of motion will be measured, followed by the timed up and go, and 15 meters walk test.

Adverse events will be investigated to determine potential causality including wound infection, prosthetic failure, periprosthetic fracture or other medical complications. The PI will be responsible for auditing and the trial conduct. Details of the surgical approach, surgeon, prostheses and post-operative complications will be documented.

2.8 Statistical analysis:

The statistical Package for Social Sciences (SPSS) will be used (SPSS 23, IBM Corp., Armonk, NY, USA). The demographic data will be reported using descriptive statistics. The two groups will be compared using mixed model ANOVA to investigate effect of time and group (Field, 2010; Pallant, 2010). Loss of follow-up will be compensated using an intention to treat analysis (Heritier, Gebski and Keech, 2003). An imputation method will be used to

account for missing data (Farhangfar, Kurgan and Dy, 2008). The difference will be considered statistically significant if $p < 0.05$. The results of the timed up and go test will be interpreted using the test's published data (Rose, Jones and Lucchese, 2002).

3. Discussion:

The study will introduce a novel exploration of articular mobilization, specifically MWM, to optimize rehabilitation for TKA. Articular mobilization techniques have demonstrated their effectiveness in managing different orthopedic conditions (Hoving et al., 2002; Collins, Teys and Vicenzino, 2004; Senbursa, Baltaci and Atay, 2007; Vicenzino, Paungmali and Teys, 2007; Yang et al., 2007; Do Moon et al., 2005). TKA alters knee kinematics and reduces lateral femoral condyle posterior translation and tibial medial rotation (Stiehl et al., 1995; Li et al., 2004; Zelle, Van der Zanden and De Waal Malefijt, 2009), which could be considered one of the main factors for reduced knee flexion. However, the success of MWM has not been explored previously for the rehabilitation of TKA. The therapeutic concept of MWM for correcting joint accessory movement to enhance the physiological movement, such as knee flexion, could theoretically be an important addition to enhance the rehabilitation for TKA.

The study will employ a single-blind randomized controlled trial design which is a robust design for examining the effectiveness of an intervention. Additionally, the three elements of the ICF have been considered (World Health Organization, 2002). The internal validity of the current study is enhanced by utilizing reliable and valid outcome measures using standardized procedures. However, due to the nature of the intervention, it is not possible to blind the patients, which might risk the results to bias. The study will only include women so it will not be possible to generalize to men. The findings could have a significant impact in the rehabilitation of TKR, leading to more satisfactory outcomes in terms of reducing pain and improving mobility, which could positively impact activity and participation.

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Figure 1: CONSORT flow diagram for reporting patients' enrollment, allocation and follow-ups.

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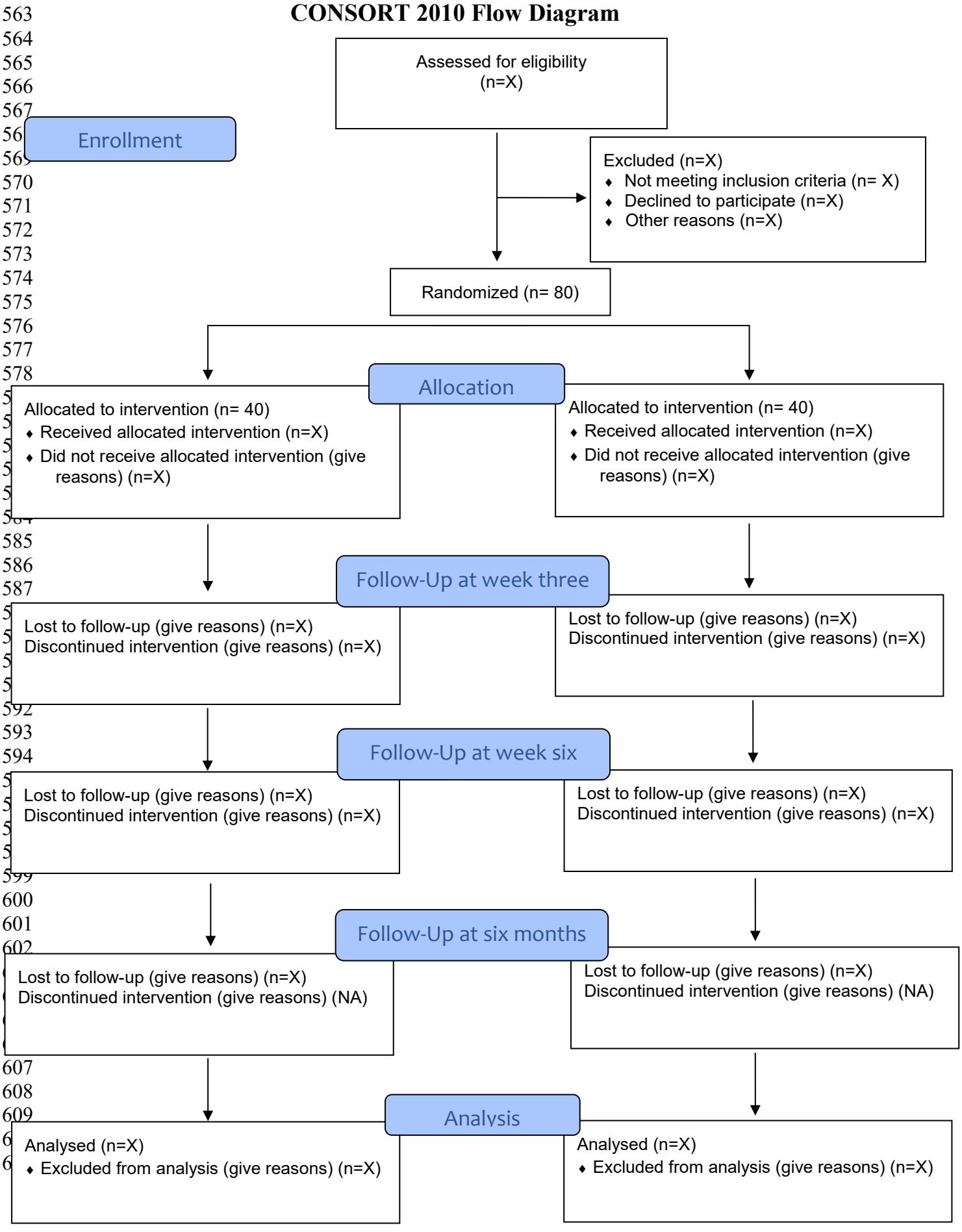
CONSORT 2010 Flow Diagram
Assessed for eligibility (n=X)
Enrollment
Excluded (n=X)
Not meeting inclusion criteria (n= X)
Declined to participate (n=X)
Other reasons (n=X)
Randomized (n= 80)
Allocation
Allocated to intervention (n= 40)
Received allocated intervention (n=X)
Did not receive allocated intervention (give reasons) (n=X)
Allocated to intervention (n= 40)
Received allocated intervention (n=X)
Did not receive allocated intervention (give reasons) (n=X)
Follow-Up at week three
Lost to follow-up (give reasons) (n=X)
Discontinued intervention (give reasons) (n=X)
Lost to follow-up (give reasons) (n=X)
Discontinued intervention (give reasons) (n=X)
Follow-Up at week six
Lost to follow-up (give reasons) (n=X)
Discontinued intervention (give reasons) (n=X)
Lost to follow-up (give reasons) (n=X)
Discontinued intervention (give reasons) (n=X)
Follow-Up at six months
Lost to follow-up (give reasons) (n=X)
Discontinued intervention (give reasons) (NA)
Lost to follow-up (give reasons) (n=X)
Discontinued intervention (give reasons) (NA)
Analysis
Analysed (n=X)
Excluded from analysis (give reasons) (n=X)
Analysed (n=X)
Excluded from analysis (give reasons) (n=X)