OBES SURG (2014) 24:1875–1880
DOI 10.1007/s11695-014-1280-4

ORIGINAL CONTRIBUTIONS

Recruitment and Screening for a Randomized Trial Investigating Roux-en-Y Gastric Bypass versus Intensive Medical Management for Treatment of Type 2 Diabetes

Avis J. Thomas · Heather A. Bainbridge · Joyce L. Schone · Shu-Chun Chen · John E. Connett · Sayeed Ikramuddin · Wei-Jei Lee · Michael D. Jensen · Daniel B. Leslie · Judith Korner

Published online: 27 May 2014

Abstract
Background Large-scale randomized clinical trials are needed to assess the role of Roux-en-Y gastric bypass (RYGB) in treating patients with type 2 diabetes mellitus (T2DM). Recruitment challenges must be understood.
Methods One hundred twenty participants were needed for a prospective randomized controlled trial investigating treatments for hyperglycemia and cardiovascular disease risk factors in patients with T2DM. The trial had two arms—intensive medical management plus a rigorous lifestyle intervention (LS/IMM) versus LS/IMM with RYGB. Medical inclusion criteria included glycosylated hemoglobin (HbA1c) ≥8.0 % while under the care of a physician and body mass index (BMI) 30.0–39.9 kg/m^2. Another inclusion criterion was expressed willingness to accept randomization and participate fully. Varied recruitment strategies were employed at four academic hospitals in the USA and Taiwan, including referrals, mass media, direct mail to patients drawn from a practice-based database, and direct mail to commercial mailing lists.
Results Between February 2008 and December 2011, 2,648 candidates were phone-screened and 240 were screened on site; 120 participants were eventually randomized. Impediments included stringent medical inclusion criteria and a lack of equipoise (i.e., strong beliefs or preferences) among patients and their personal community-based physicians. To meet timeline requirements, the upper limit for BMI was increased from 34.9 to 39.9 kg/m^2 and an additional site was added.
Conclusions We successfully recruited 120 participants with poorly controlled T2DM and mild to moderate obesity. Participants had to be willing to accept randomization to either surgical or nonsurgical treatments. Recruitment took 4 years.

Keywords Type 2 diabetes mellitus · Bariatric surgery · Metabolic surgery · Roux-en-Y gastric bypass · Recruitment · Randomized clinical trial

Abbreviations

BMI	Body Mass Index
CUMC	Columbia University Medical Center in New York, NY
DSS	Diabetes Surgery Study
HbA1c	Glycated Hemoglobin
Taiwan	Two closely related clinics in Taiwan
T2DM	Type 2 diabetes mellitus
Mayo	Mayo Clinic in Rochester, MN
UMN	University of Minnesota in Minneapolis, MN

This study was supported by a research grant from Covidien.

A. J. Thomas (✉) · J. E. Connett
Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA
e-mail: avist@ccbr.umn.edu

H. A. Bainbridge · J. Korner
Department of Medicine, Columbia University Medical Center, New York, NY, USA

J. L. Schone · S. Ikramuddin · D. B. Leslie
Department of Surgery, University of Minnesota, Minneapolis, MN, USA

S.-C. Chen · W.-J. Lee
Department of Surgery, Min-Sheng General Hospital, Taoyuan, Taiwan, Republic of China

M. D. Jensen
Endocrine Research Unit, Mayo Clinic, Rochester, MN, USA

A. J. Thomas
Institute for Education and Research, Health Partners, Bloomington, MN, USA

Introduction

Type 2 diabetes mellitus (T2DM) has emerged as a rapidly growing global epidemic. Conventional medical management often fails. The diabetes epidemic is partially fueled by an obesity epidemic, which is likewise refractory to conventional treatment [1]. However, research has begun to suggest that metabolic surgery may be a valuable component of T2DM treatment plans. A meta-analysis showed that metabolic surgery dramatically improves diabetes in 78 % of those with body mass index (BMI) ≥35 kg/m^2 [2]. An observational study of 66 patients with T2DM and BMI of 30–35 kg/m^2 showed remission of diabetes in 88 % of the patients 5 years after surgery and substantial reductions in cardiovascular disease risk factors [3].

In response to the T2DM epidemic and increased evidence, expert panels have begun to expand treatment recommendations. The International Diabetes Federation's 2011 position statement [4] acknowledged bariatric surgery as an appropriate treatment for T2DM when glycemic targets are not otherwise achievable. The statement recommended that bariatric surgery be included in future treatment guidelines [5]. The American Diabetes Association's (ADA) 2013 Standard of Care attributes B-level evidence to the use of metabolic surgery in patients with BMI >35.0 kg/m^2 but finds insufficient evidence for recommending bariatric surgery in patients with BMI <35 kg/m^2 outside of research protocols [6]. There is a clear need for A-level evidence regarding the effectiveness of metabolic surgery in patients with T2DM and BMI's both above and below 35 kg/m^2.

The Diabetes Surgery Study (DSS) [7] and randomized studies by Dixon et al. [8], Mingrone et al. [9], and Schauer et al. [10] have recently begun to address the need for randomized controlled trials in this area. However, further randomized studies are needed. This paper describes the recruitment hurdles faced by the DSS and how they were overcome.

Methods

As described elsewhere [8], the DSS is a randomized controlled trial (RCT) testing two alternative treatments for patients with T2DM. One hundred twenty patients were randomized one-to-one to two treatment regimens. The first arm was rigorous conventional treatment (LS/IMM), consisting of an intensive lifestyle intervention modeled after the LookAHEAD trial [11] and intensive medical management using FDA-approved pharmacotherapy for T2DM, blood pressure, lipids, and obesity. The second arm was RYGB plus LS/IMM. The primary endpoint was assessed at 1 year and consisted of the simultaneous resolution of three cardiovascular disease risk factors—glycosylated hemoglobin (HbA1c) <7.0 %, systolic blood pressure (SBP) <130 mmHg, and low density lipoprotein serum cholesterol (LDL) <100 mg/dL. The active intervention continued for a second year, after which secondary endpoints were examined. Annual observational-only follow-up visits continue in years 3–5, supporting further secondary endpoints. The DSS is registered with the National Institutes of Health as NCT00641251. The study was approved by each site's Institutional Review Board (IRB) and Taiwan's Department of Health (DOH). All subjects provided signed informed consent.

Key inclusion criteria were as follows:

1. Age 30–67 years.
2. BMI 30.0–34.9 kg/m^2 (prior to December 2009) or 30.0–39.9 kg/m^2 (after December 2009).
3. HbA1c ≥8.0 and ≤14.0 % despite being under the active medical care for T2DM for at least 6 months prior to enrollment.
4. Stimulated serum C-peptide >1.0 ng/mL.
5. Ability and willingness to accept either randomization assignment and follow all study requirements for that arm.
6. Completion of a 2-week assignment requiring patients to record food, exercise, and serum glucose levels.
7. Absence of any medical or psychiatric conditions that would contraindicate surgery or impede protocol compliance.

Site Recruitment

Criteria for sites included the ability to recruit and retain participants and strengths in RYGB, diabetes management, and lifestyle interventions. All US sites were Bariatric Surgery Centers of Excellence; that requirement was waived for Taiwan where no such program exists. The study's principle investigator, who is a bariatric surgeon, vetted each surgical team carefully.

Patient Recruitment

Recruitment began at the University of Minnesota (UMN), Columbia University Medical Center (CUMC), and in Taiwan (Taiwan) from early 2008 to July 2009. The Mayo Clinic in Rochester, Minnesota (Mayo) joined the study in April 2010 to accelerate recruitment. Recruitment ended in December 2011 when the 120 patient goal was reached.

The sites used a wide variety of recruitment strategies to attract participants. Emphasis was placed on finding individuals who met medical criteria and were willing to be randomized and fully participate in the study regardless of the treatment arm.

Recruitment at the University of Minnesota

Substantial effort was spent on outreach to medical providers both inside and outside the UMN's own institution. Providers included doctors specializing in primary care or endocrinology, staff at the bariatric surgery clinic, other in-hospital staff, diabetes educators, and staff at Native American clinics. UMN staff met with providers in their own clinics to explain the study protocol. Information and flyers were mailed to the clinics. The hospital newsletter published a feature article.

Investigators ran four radio advertisement campaigns, each 1–3 weeks long. Three newspaper advertisements were published—two in the city's two primary newspapers and one in the university's free campus paper.

Other recruiting efforts included four mass mailings using purchased lists of patients who self-reported T2DM in health surveys, flyers at the UMN and in other clinics, posting on the university's bariatric surgery website, and informational meetings or booths at health fairs throughout the city (including the ADA's Diabetes Expo, diabetic support groups, Minnesota State Fair, the Mexican consulate and Native American clinics and community events). Additional candidates learned of the trial via ClinicalTrials.gov or by word of mouth.

Recruitment in Taiwan

Investigators in Taiwan relied on referrals from their own outpatient clinics, referrals from other doctors and flyers posted at the hospital. Investigators introduced the DSS to colleagues one-to-one and in several informal seminars held from July 2009 to July 2010. The seminars presented surgical and medical treatments for T2DM and introduced the study. Taiwan's Department of Health (DOH) prohibits recruiting via mass media, mailing lists, media events, formal group presentations, or news features. The DOH further encumbered the study by requiring 24 months to provide administrative approval for the protocol.

Recruitment at Columbia University Medical Center

CUMC placed 37 advertisements in a variety of papers, including major newspapers, neighborhood papers, the hospital's newsletter, and both free and for-purchase commuter daily newspapers. Nine one-week radio advertising campaigns were run around the clock, during both peak and off-peak hours. Yields were enhanced by running the same advertisement repeatedly. Short-duration intensive campaigns proved more successful than spacing ads over time.

Other efforts included outreach at an ADA Diabetes Expo, a direct mail campaign using a purchased mailing list, letters to local endocrinologists, informational meetings with local clinics, flyers placed throughout the hospital and outpatient offices, and informational cards at professional meetings. Internet advertising included Craig's List, Clinical Connection, ClinicalTrials.gov, and a posting on CUMC's bariatric surgery center's website.

Recruitment at Mayo Clinic

Researchers at Mayo Clinic used a practice-based database to identify primary care patients who met key inclusion criteria at their last medical visit—age, T2DM diagnosis, HbA1c ≥8.0 %, and BMI 30.0–39.9 kg/m^2. Letters were mailed to over 500 patients informing them of the study and providing information on how to learn more. Flyers were posted in various outpatient clinics and information about the study was shared with other Mayo Clinic physicians.

Screening

Candidates underwent a rigorous screening process aimed at assuring they were appropriate for the study, gave informed consent and were likely to remain in the study for the full 2-year intervention. Candidates initiated phone contact with the clinics. Clinic coordinators conducted scripted screening interviews by phone, with easier questions placed at the beginning. If patients did not qualify, coordinators recorded the first criterion failed. If the candidate appeared eligible, coordinators explained the study, along with the major risks and drawbacks of surgery and the commitment required for the intensive lifestyle intervention. After expressing willingness to accept randomization to either arm and comply with all study requirements, candidates were mailed an informed consent document and a "study agreement" and invited to the clinic for further screening. The study agreement was a one-page document outlining the commitments they would be asked to make. Prospective participants signed the informed consent and the study agreement upon arrival at the clinic. The potential risks and benefits of RYGB were explained again, and patients were encouraged to opt out of the trial if they did not feel comfortable with either arm. Candidates were asked to participate in a 2-week run-in exercise in which they logged their food, exercise, and glucose readings. If they failed to keep the 2-week log, they were excluded from the study.

To reconfirm informed consent, candidates invited to the randomization visit were asked for a response to the following five items: (1) Please say in your own words what the trial is about and what the treatments are in each arm; (2) Please describe the major risks of surgery; (3) Are you willing to take the risk of surgery?; (4) Please describe the 2-year commitment you are being asked to make; (5) Are you willing to make the requested 2-year commitment, as described in the Study Agreement? If all five items had acceptable answers,

the candidate was randomized. The intervention started as soon as possible in order to engage participants quickly and minimize early drop-outs.

Compensation

The study's sponsor paid for all study-related surgeries and medical care and the 38-visit intensive lifestyle intervention. Study-related medications were billed to insurance whenever possible; the sponsor paid for any drugs not covered by insurance and also covered co-pays whenever allowed by law. UMN participants received compensation for parking; compensation for transportation costs was also provided on request. Participants in Taiwan received $30 US for completed screening and for visits at months 6, 12 and 24. Participants at CUMC received $25 for each completed visit, which was sufficient to cover parking. Active participants at Mayo were paid $400 upon completion of the 24-month visit.

Results

Participants came from a variety of sources (Table 1). A total of 2,648 candidates were screened in order to obtain 120 randomizations (22 screens per randomization). Yield rates varied by site and were better for sites that were able to rely on referrals or a practice-based database rather than mass media. UMN and CUMC experimented with a variety of recruiting sources; their most productive sources were referrals and mass media, respectively.

Screening results are summarized in Fig. 1. Of 2,648 candidates screened by phone, 1,823 (69 %) were excluded due to age, circumstances, BMI or HbA1c; of these, BMI (39 %), and HbA1c (17 %) were the largest. Of the remaining 825 candidates, 479 (58 %) declined and finally 227 were excluded for other reasons. It was often difficult to identify a single rationale for the 479 candidates who declined. However, roughly equal numbers were unwilling to be randomized to the surgical and non-surgical arms. Half of the 240 candidates who attended on-site screening visits were randomized (data not shown).

Prior to December 2009, 22 % of the 900 candidates screened were excluded due to BMI between 35.0 and 39.9 kg/m^2. After the BMI, range was expanded to 30.0–39.9 kg/m^2; these candidates were revisited, only two were randomized as a result. The reasons for continued exclusion were approximately equally divided among (a) could not be contacted, (b) had lost interest, and (c) failed other criteria. Seventy percent of the participants randomized under the liberalized criteria (and 38 % of all randomized participants) had BMI 35.0–40.0 kg/m^2. Liberalizing the BMI criteria had little effect in Taiwan because few Taiwanese candidates were in that size range.

Table 1 Counts of phone screens and randomizations, by site

	UMN	Taiwan	CUMC	Mayo	Total
Phone screens	942	369	1,241	96	2,648
Randomizations	49	32	29	10	120
Phone screens per randomization	19	12	43	10	22
Randomizations by recruitment source[a]					
Referrals					
From DSS clinicians' own practice	7	14	0	–	21
From DSS clinicians' institutions	2	7	0	–	9
From outside medical practices	16	–	0	–	16
Mass media					
Radio advertisement	8	–	15	–	23
Newspaper advertisement	4	–	9	–	13
Television news feature	3	–	–	–	3
Direct mail campaigns					
Purchased mailing list	7	–	1	–	8
Practice-based database	–	–	–	10	10
Posters and flyers on site	0	11	2	0	13
Internet-based					
ClinicalTrials.gov	1	–	2	–	3
Craig's List, Clinical Connections	–	–	0	–	0
Institution's bariatric surgery webpage	0	–	0	–	0
Public events	0	–	0	–	0
Word of mouth	1	–	0	–	1
Total randomizations	49	32	29	10	120

[a] 0 indicates that no randomized patients came from this source; "–" indicates that the site did not use this source

Discussion

Recruitment took nearly 4 years and was more difficult than expected. Because of the slow recruitment rate, the study broadened the BMI inclusion criteria from 30.0 – 34.9 to 30.0–39.9 kg/m^2 and added an additional site. A total of 2,648 prospective recruits were screened to obtain 120 randomized participants (22 per randomization). Major hurdles included finding candidates who were in the desired BMI and HbA1c ranges and willing to accept randomization. Some would not accept RYGB, some would not participate unless they underwent RYGB and some could not commit to the intensive lifestyle intervention.

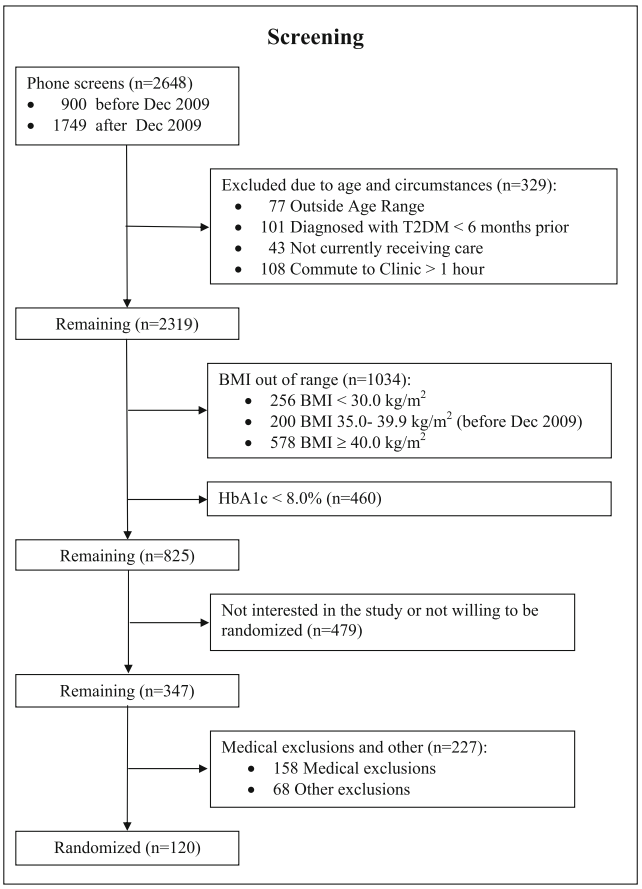

Fig. 1 Screening

Many prospective candidates and potential referring physicians had strong beliefs, preferences, or value-based assessments regarding metabolic surgery. There may have been additional skepticism regarding patients with BMI 30.0–34.9 kg/m^2. This increased the difficulty of finding patients willing to be randomized and physicians willing to refer them. Furthermore, emphasis was placed on screening out patients with strong preferences or biases in order to prevent future drop-outs and cross-overs. There was particular concern about patients who were randomized to LS/IMM but had insurance coverage and met their insurance plan's criteria for surgery.

Complex and demanding inclusion criteria were needed to assure patient safety and diabetic status. These criteria also slowed participant recruitment. Telephone prescreening enhanced efficiency by quickly eliminating candidates who were not willing to accept randomization and participate fully or who failed medical criteria.

For many patients, their poorly controlled diabetes and desire for good health may have been powerful incentives. The offer of free LS/IMM care and a 50 % chance for a free RYGB may have enhanced recruitment, particularly for individuals who lacked insurance, did not meet insurance requirements for surgery, or had high co-pays.

A variety of recruiting techniques were tried; their relative effectiveness varied by site. The most successful strategies were (in order):

1. Referrals (UMN, Taiwan)
2. Mass media (UMN, CUMC)
3. Direct mail (UMN, Mayo).

The strategies with the lowest yield for the effort and expense were:

1. Outreach at community events (UMN and CUMC)
2. Referrals (CUMC)
3. Direct mail (CUMC).

Passive sources (flyers and internet-based strategies) produced few candidates in the USA. However, they were cost-effective because they required few resources. Physician referrals and candidates from the clinically based database had high probability of being randomized; candidates recruited via mass media were much more likely to be screened out.

Sung et al. [12] report that difficulty in finding willing participants is a common problem across most RCTs. McDonald reports that only 31 % of randomized clinical trials complete recruitment within the initial timeline and 53 % are granted an extension [13]. The study's 4-year recruitment period was thus in accordance with broader clinical trials experience. Three other groups of researchers have successfully recruited for trials randomizing lower BMI patients with type 2 diabetes to bariatric surgery versus medical management. Dixon et al. [8] recruited 60 patients in Melbourne, Australia over 2 years (2002–2004). Participants had recently diagnosed diabetes (<2 years) and BMI 30–40 kg/m^2. Mingrone et al. [9] recruited 72 patients in Rome over 2.5 years (2009–2011). They included patients with HbA1c >7.0 % (versus 8.0 % for the DSS). Schauer et al. [10, 14] recruited 150 patients to a study at Cleveland Clinic over a 3-year period (2007–2010). They included patients with HbA1c >7.0 %, had an expanded BMI range of 27–43 kg/m^2 (versus 30–39.9 kg/m^2 for the DSS), and did not require candidates to be under the care of a doctor. The DSS's recruitment rate was thus in line with that of other successful studies in this area.

Recruitment difficulties present a substantial impediment to future randomized trials. Recruitment could have been accelerated by enrolling more sites early in the study and by increasing the advertising budget where needed. Prospective sites should be screened for their ability to recruit patients who meet medical criteria and are truly willing to be randomized to either arm. Prospective sites are more likely to succeed at cost-effective recruitment if they have strong relationships with local endocrinologists who are willing to refer eligible patients to the study. A

large in-house database of patients is also an asset. Prospective sites also need to be able to make the study as convenient for patients as possible, by providing parking, dovetailing medical, lifestyle, and surgical follow-up visits, and if possible providing compensation for transportation and missed time at work.

If long-term randomized comparisons are of interest, sites should give lower priority to recruitment from patient populations already seeking surgery. Such patients may be less likely to accept a nonsurgical randomization assignment long term. An alternative would be to propose a fixed follow-up period and offer patients surgery after that time, if surgery proves beneficial. This facilitates recruitment but affects longer-term randomized comparisons. In addition, patients may have difficulty waiting, or may not adhere as closely to the nonsurgical treatments if they know another alternative is coming.

Conclusion

Over a 4-year period, the DSS successfully recruited and randomized 120 participants. Liberalizing the BMI criteria from 30.0–34.9 kg/m^2 to 30.0–39.9 kg/m^2 and adding an additional site accelerated recruitment.

The DSS's cohort of 120 randomized participants will provide valuable insight into the possible role of metabolic surgery as a treatment for T2DM. Cohorts like this will be rare because of the difficulty in obtaining them.

Conflict of interest statements All authors except for Dr. Leslie received salary support from Covidien for conducting the study and reporting results. Ms. Thomas, Ms. Bainbridge, Ms. Chen, Dr. Connett, Dr. Lee, Dr. Leslie and Ms. Schone have nothing further to disclose. Dr. Ikramuddin further reports personal fees from Novo Nordisk, personal fees from Medica, personal fees from OptumHealth, personal fees from Metamodix Inc, personal fees from Covidien, grants from EnteroMedics, and grants from Reshape Medical. Dr. Jensen further reports personal fees from Novo-Nordisk, personal fees from Eisai, and personal fees from Vivus. Dr. Korner further reports personal fees from Johnson and Johnson, personal fees from Nutrisystem, personal fees from Federal Trade Commission, and personal fees from Office of Professional Misconduct.

References

1. Ryan DH, Kushner R. The state of obesity and obesity research. JAMA. 2010;304:1835–6.
2. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:724–37.
3. Cohen RV, Pinehiro JC, Schiavon CA, et al. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. Diabetes Care. 2012;35:140–8.
4. International Diabetes Federation Taskforce on Epidemiology and Prevention. Bariatric surgical and procedural interventions in treatment of obese patients with type 2 diabetes. 2011. www.idf.org/webdata/docs/IDF-Position-Statement-Bariatric-Surgery.pdf. Accessed 18 July 2012.
5. Zimmet P, Alberti KG. Surgery or medical therapy for obese patients with type 2 Diabetes? N Engl J Med. 2012;366:1635–6.
6. American Diabetes Association position statement. Standards of medical care in diabetes—2013. Diabetes Care. 2013;36:S11–66.
7. Ikramuddin S, Korner J, Lee WJ, et al. Roux-en-Y gastric bypass versus intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia. The Diabetes Surgery Study Randomized Clinical Trial. JAMA. 2013;309(21):2240–9.
8. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299:316–23.
9. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012;366:1577–85.
10. Schauer PR, Kashyan S, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012;366:1567–76.
11. Ryan DH, Espeland MA, Foster GD, et al. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. Control Clin Trials. 2003;24:610–28.
12. Sung N, Crowley WF, Genel M. Central challenges facing the national clinical research enterprise. JAMA. 2003;289:1278–87.
13. McDonald AM, Knight RC, Campbell MK, et al. What influences recruitment to randomized controlled trials? A review of trials funded by two UK funding agencies. Trials. 2006;7:9.
14. Kashyap Sangeeta R, Bhatt Deepak L, Schauer Philip R, et al. Bariatric surgery vs. advanced practice medical management in the treatment of type 2 diabetes mellitus: rationale and design of the Surgical Therapy And Medications Potentially Eradicate Diabetes Efficiently trial (STAMPEDE). Diabetes Obes Metab. 2010;12:452–4.