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**LONG-TERM OUTCOMES OF TRANSOBTURATOR TAPES IN WOMEN WITH
STRESS URINARY INCONTINENCE; E-TOT RANDOMISED CONTROLLED TRIAL**

Running title: Long-Term Outcomes of Transobturator Tapes in Stress Urinary Incontinence

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Abstract

Objectives: To assess the long-term (LT) patient-reported outcomes and adverse events(AE) following transobturator tension-free vaginal tape(TO-TVT)

Design: Postal follow-up of the E-TOT randomised controlled trial(RCT)

Setting: A tertiary urogynaecology center in the UK; all procedures took place in 2005 to2007.

Population: 341 Women were randomised to undergo either “inside-out” TVT-O (Ethicon Inc.,Somerville,NJ,USA) or “outside-in” TOT-ARIS (Coloplast Corp., Minneapolis,MN,USA).

Methods: Long-term (median 9-years) follow-up, using validated symptom severity and QoL questionnaires. Statistical analysis was performed using SPSS v22.0(IBM Corp.,Armonk, NY,USA) and GraphPad Statistics-2014.

Main Outcome Measures: Primary outcome was patient-reported success rate defined as “Very Much/Much Improved” on the Patient's Global Impression of Improvement (PGI-I) scale. Secondary outcomes included impact on women’s QoL and sexual function; adverse events and re-operations for SUI.

Results: The adjusted-response rate was 67.8%; median follow-up was 9.2-years. The overall patient-reported success rate was 71.6% with further 14% reporting “improvement”; and no significant difference between inside-out and outside-in groups ($p=0.76, OR:0.8676, 95\%CI:0.4744, 1.5865$). The success rate showed significant reduction compared to 1-year results (71.6% vs.80%; $p=0.004$) but clinically insignificant reduction when compared to the 3-years (71.6% vs.73.1%). A total of 7.96 % underwent further continence surgery; tape extrusion/erosion rate was 4.5%; groin pain/discomfort was reported in 4.32% with only 1.4% requiring treatment.

Conclusions: This is the largest and longest follow-up randomized trial of TO-TVT. TO-TVT is associated with 71.6% patient-reported success rate, 4% groin pain/discomfort and 8% continence re-operation rate at median of 9-years follow-up. The success rate is almost stable after 3-years.

Keywords: ARIS, tension-free vaginal tapes, transobturator tape, TVT-O, Stress urinary incontinence.

Tweetable abstract: The success rate for TO-TVT is 71% at 9-years and is almost stable after 3-years; 8% required repeat surgery.

Trial registration number and link to the registration web page: The study was registered on www.clinicaltrials.gov and registration number is: NCT00136071. The registration web page link is: <https://clinicaltrials.gov/ct2/results?term=NCT00136071&Search=Search>

Introduction:

There is a paucity of data on the long-term outcomes of transobturator tension free vaginal tape (TO-TVT) in the surgical treatment of female stress urinary incontinence (SUI). In the UK, the National Institute for Health and Clinical Excellence (NICE)¹ and the interim reports on transvaginal mesh for SUI and prolapsed surgery, both in Scotland² and England³ highlighted the lack of long-term outcomes data for mid-urethral slings(MUS) in general and TO-TVT in particular. They emphasized the importance of directing future research to address this gap in the literature. Long-term data on MUS are primarily derived from the clinical trials assessing retro-pubic tension-free vaginal tapes (RP-TVT)^{4,5} however long-term outcomes for TO-TVT are now emerging^{6,7}.

The E-TOT⁸ is the largest RCT assessing the outcomes of TO-TVT (n=341 women); and the only adequately powered RCT in the literature to compare inside-out versus outside-in approaches. We have previously reported the outcomes at 1 and 3-years follow-up^{8,9}. At 3-years, the patient reported success rate, was 73.1% with no significant difference between groups (Inside-out 73.18% vs. Outside-in 72.3%; OR: 0.927; 95%CI 0.552–1.645; p=0.796)⁹. In the E-TOT study we used the Patient Global Impression of Improvement (PGI-I) as the primary outcome as it provides a robust, validated and more global review of the treatment outcome, and more fully encompassing the range of benefits and potential harms of the treatment. Several studies have established its validity to assess disease severity, bother and improvement after treatment in women with SUI.

In this study we aim to assess the long-term (LT) outcomes and adverse events (AE) following TO-TVT as a whole cohort and to compare the effectiveness of inside-out versus outside-in approaches.

Methods:

Long-term (LT) follow-up of the E-TOT RCT (Fig1) conducted between April-2005 and April-2007 in a tertiary urogynaecology center in the UK. The E-TOT protocol was registered on www.clinicaltrials.gov and ethics committee approval was obtained for this LT follow-up. All eligible participants with urodynamic SUI or stress predominant mixed UI, who failed or declined pelvic floor muscle training and opted for a MUS procedure, within the study period, were invited to participate. Women with pelvic organ prolapse (\geq POP-Q stage-2), concomitant surgery, previous pelvic irradiation, relevant neurological conditions (such as multiple sclerosis) were excluded.

Participants (n=341) were randomised to undergo either TVT-O(Ethicon Inc.,Somerville, NJ,USA) for the inside-out approach or TOT-ARIS(Coloplast Corp.,Minneapolis, MN,USA) for the outside-in approach. TO-TVT was performed as originally described.^{10,11} Preoperative assessment included urodynamic assessment and completion of the Birmingham Bowel Urinary Symptom-22 questionnaire¹²; King's Health Questionnaire (KHQ)^{13,14} and Prolapse Incontinence Sexual Function Questionnaire (PISQ-12)¹⁵. At 1,3 and 9-years follow-up, participants were contacted by post and completed the above questionnaires and in-addition, PGI-I¹⁶; International

Consultation on Incontinence Questionnaire-Short Form(ICIQ-SF)¹⁷; Urgency Perception Scale(UPS)¹⁸; questions on adverse events(AE) and further continence surgery.

Total of 314 participants were included in this LT follow-up; 22-participants who received further continence surgery within the first 3-years were included in this study and considered as failures. 292-participants were contacted between April-2014 and February-2015. Strategy for non-responders included another round of postal questionnaire. Persistent non-responders received a further short questionnaire and/or phone interview.

Similar to 1 and 3-years reports, the primary outcome was patient-reported success rate based on a response of “Very/Much Improved” to the PGI-I. Secondary outcomes were further continence surgery; impact on quality of life (QOL); sexual function; AE such as groin/thigh pain and tape erosions/extrusions; and risk factors for late failures.

We anticipated $\geq 50\%$ response rate; assuming 180 respondents (90 in each arm) and a success rate of 70% for inside-out TVT-O, as reported by Angioli et al¹⁹, this would allow 80% power to detect a 20% difference in the patient-reported success rates between the two groups. Categorical variables were compared using chi-square test. Within-group comparison was undertaken using Wilcoxon and Mann-Whitney tests. Risk factors for late failures were assessed in a sequential regression model. All statistical analysis was performed using SPSSv.22.0 (IBM Corp.,Armonk,NY,USA)and GraphPad Statistics 2014.

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Results:

314 participants were included in this LT study; 7 participants were excluded (deceased n=4 and withdrawn n=3). LT follow-up was completed by 208 (Outside-in n=104 vs. Inside-out n=104); the adjusted response rate is 67.8% (Figure 1). The mean age at follow-up was 61-years /SD10.12 (median59; range41-87). The median follow-up was 9.2-years (range 81-119month; mean 109.8month /SD15.22). All missing data were confirmed to be missing at random and were handled by multiple imputation and sensitivity analysis. .

- **Patient-Reported Success:** The overall patient-reported success rate, defined as Very/Much Improved on PGI-I, was 71.6% with no significant difference between groups (Outside-in 73.1%(n=76) vs Inside-out 70.2%(n=73); p=0.76; OR:0.867, 95% CI:0.474, 1.586). A further 14% (n=30) reported “Improvement”. These results pertained on random multiple imputation and multiple sensitivity analysis (Table 1). The patient-reported success rate using last observation carried forward for missing data was 72.6% with no significant differences between groups (Outside-in 75.5% vs Inside-out 69.9%; p=0.29) (Table 1).

Compared with the 1-year outcomes, there was a significant reduction in the patient-reported success rate at 9-years (80% versus 71.6%, p=0.004). However compared to the 3-years follow-up, there was only a modest 1.5% reduction over 6-years (73.1% versus 71.6%) (Figure 2a). A number of potential risk factors for “late failure” (i.e. period between the 3 & 9-years follow-up)

were analysed including age, BMI, OAB symptoms, previous continence surgery and MUCP; no independent risk factors were identified on sequential regression analysis.

Further analysis for women within who did not meet the definition of success (n=59) showed PGI-I responses of “Improved(n=30)”, “Same(n=10)”, “Worse(n=10)”, “Very Much Worse(n=9)”. We further analyzed ICIQ-SF and BBUQ-22 responses in this group, this showed symptoms of MUI in 47 women, symptoms of pure UII and pure SUI in 3 and 4 women respectively.

• **Adverse events (AE):** AE were assessed amongst the respondents only (n=208) and showed: 9.61% de-novo urgency rate of which (84%) were mild or moderate on UPS. Late tape extrusion/ erosions i.e. after 3-years was reported in 1.9% (n=4). However the total erosion/extrusion rate over the period of follow-up, in the whole E-TOT cohort is 4.5% (n=14/314).

Groin or inner thigh pain/discomfort (defined by the patient having any level of thigh and/or groin pain/ discomfort) were reported in 4.32% (Inside-out n=4 vs. Outside-in n=5): two participants (1%) reported to be receiving analgesia while one participant (0.4%) underwent complete tape removal for a combination of vaginal extrusion and pain. The latter participant reported a background of arthritis for which she was also receiving analgesia. Table 2 shows all AE at 9 years.

Further Continence Surgery: A total of 25 participants (7.96 %) underwent further surgical treatment for SUI over the entire follow-up period in the whole E-TOT cohort (n=25/314). However only 1% (n=3) underwent repeat surgery between the 3 and 9-years follow-up (Figure 2b). The surgical details of the repeat continence surgery and their outcomes are presented in Table S1: the patient-reported success rate in this group was relatively poorer (65%) however it was difficult to draw meaningful analysis due to the relatively small cohort and the heterogeneity of the type of further continence surgery performed.

QoL and Sexual Function: KHQ was completed by 171 participants. Clinically significant improvement in QoL (defined as ≥ 10 points improvement) was seen in 76.8% with no evidence of significant differences between both groups (OR 0.566; 95% CI 0.292-1.202; p=0.121). 87 participants (44.8%) completed PISQ-12 questionnaires (both pre and post-operative). The sexual function score on PISQ-12 showed improvement in 61% and deterioration in 34.5% with no evidence of significant difference between groups (p=0.113) Table S2.

DISCUSSION:

The E-TOT study is the largest RCT to report long-term outcomes for TO-TVT with the ability to compare the patient-reported outcomes at different follow-up points.

Main Findings: The results show that the overall patient-reported success rate of TO-TVT was 71.6% at median follow-up of 9-years, with no significant difference between groups; the results pertained on multiple sensitivity analyses. Further 14% reported “Improvement” however unlike Nilsson et al⁵, we did not consider “improved” as a successful outcome to avoid over-estimation of success rates. Nilsson et al⁵ reported on a small population (n=58) who underwent RP-TVT with 17years follow-up; the patient-reported success rate was 87%. The success rate showed significant reduction compared to 1-year results but clinically insignificant reduction when compared to the 3-years. Clinically significant improvement in QoL was seen in the majority of patients (76.8%) with no evidence of significant differences between both groups. A total of 8% underwent further continence surgery. Adverse events included: tape extrusion/ erosion rate was 4.5%; groin pain/discomfort in 4.32% with only 1.4% requiring treatment.

Strengths and Limitations

The LT follow-up for a large homogenous cohort of women and the clinically applicable results are major strengths. The good response rate of 67.8% is quite representative of the whole cohort. The E-TOT RCT is adequately powered, with robust inclusion and exclusion criteria and standardized postoperative assessment using validated tools. Patient reported outcomes were obtained by postal questionnaire which essentially eliminates the assessor’s bias and reduces the participants’ visits to hospital which in-turn reduces the attrition rates.

The assessment of the AE in our study was self-reported which may be seen as a limitation, however this approach excludes the assessor bias. We acknowledge the limitation of the data

on long-term pain/discomfort - further qualitative study is required to assess those participants with pain for severity; relation to the procedure; impact on QoL and any possible regret. The single center design can be seen as a limitation however the procedures were performed by 6- surgeons of varying experience ensuring generalizability of the results. The lack of objective assessment for cure of UI is a limitation of this study.

Interpretation in light of other evidence:

The success rate in the E-TOT study is similar to RP-TVT at 10-years: Groutz et al²⁰ underwent a telephone follow-up at 10-years and reported an overall patient-reported success rate of 65% while 78% reported cure of SUI. Similarly, Aigmueller et al²¹ assessed 140 women at 10-years following RP-TVT and reported a patient-reported cure rate of 57% with further 23% reporting “improvement”. Svenningsen et al²² showed higher patient-reported cure rates(76%) at 10-years for a large cohort(n=483) who underwent RP-TVT.

Two recent observational studies reported the 10-years outcomes for TO-TVT: Serati et al⁷ reported the results of a multicenter study (n=160); the patient-reported and objective cure rates were 97% and 92% respectively. Their outcomes were clearly more favorable than the E-TOT study despite using the same definition of success, however inside-out TO-TVT was the only procedure performed in their study and their response rate was almost 95%. Ulrich et al⁶ reported the 10-years outcomes for inside-out TO-TVT in 2-centers (n=71); the patient-reported and objective cure rate were 64% and 69% respectively. Similarly, Zhang et al²³ showed the 7-years patient-reported success rate in the inside-out TO-TVT (n=62) to be 61.3%. Compared to the E-

TOT, the latter 2-studies used a stricter definition for patient-reported success (no leakage). We did not find any significant differences in patient-reported outcomes between inside-out and outside-in TO-TVT; this is consistent with the current literature on shorter term outcomes²⁴.

The Cochrane review²⁵ reported that the outcomes for all SUI procedures seem to decline overtime. Similar trend was seen in the E-TOT study with significant reduction in patient-reported success rate at 9-years compared to 1-year, however the outcomes were relatively stable after 3-years. Similarly, 25 participants (8%) underwent further continence surgery; of those only 1%(n=3) after the first 3-years. Based on the results of the E-TOT study, clinicians can confidently counsel women that successful outcomes at 3-years are most likely to be retained at 9-years. In the E-TOT study, the re-operation rate was similar to the 7 and 7.8% reported by Ulrich et al⁶ and Aigmueller et al²¹ in 10-years following TO-TVT and RP-TVT respectively. However, other studies have reported higher re-operation rates following TO-TVT^{19,26}.

Multivariate analysis in the E-TOT study did not show any independent risk factors for late failures. Previous continence surgery and low maximum urethral-closure pressure were independent risk factors for TO-TVT failure at 1-year follow-up⁸. Recently, Serati et al⁷ found previous continence surgery to be the only risk factor for TO-TVT failure at 10-years follow-up. Lapis et al²⁷ however showed that low-MUCP did not affect the success rates of repeat RP-TVT while a combination of low-MUCP and limited urethral mobility were associated with significantly reduced success rate.

Emphasis has been recently focused on the AE associated with the use of mesh in pelvic floor surgery. There is a general concern for possible under-reporting of AE; hence we analyzed the AE among respondents only to avoid such underestimation.

The rate of de-novo urgency in the E-TOT study was 9.6% at 9-years which were almost identical to 9.68% reported by Zhang et al²³ at 7-years follow-up for the inside-out TO-TVT. Serati et al⁷ reported a higher de-novo urgency rate (14%) at 10-years following inside-out TO-TVT, while Ulrich et al⁶ reported 26% at the same follow-up period. It's well recognized that OAB symptoms tend to wax and wane and the incidence increase with age²⁸. Hence on assessing urgency at long-term follow-up studies, it can be difficult to ascertain if it's related to the MUS or the advancing age or is a progression of an underlying pathology.

Groin Pain: In the E-TOT study, 4% of the respondents reported groin or thigh pain/discomfort and were almost equally distributed between both TO-TVT approaches; only 1.4% required either medical or surgical treatment. In some patients, the symptoms raise almost 6-7years after the operation leading to uncertainty on its relation to the procedure. The lack of a control group (without surgery) introduces further uncertainty. However chronic groin pain is a recognized AE for TO-TVT; Zhang et al²³ and Ulrich et al⁶ reported 6.4% and 9% groin/ inguinal pain/ discomfort at 7 and 10-years follow-up respectively. The current evidence therefore tends to confirm that TO-TVT are associated with long-term groin pain/discomfort. Intractable suprapubic pain has also been previously described following colposuspension and known as post-colposuspension syndrome. Interestingly, a recent long-term follow-up RCT comparing RP-TVT vs. autologous fascial slings (AFS) showed a 3.2% incidence of scar pain in the non-mesh alternative arm(AFS) , suggesting that chronic pain is not just a problem seen with mesh grafts²⁹.

Tape erosion/extrusion: our results are consistent with Ulrich et al⁶ and Zhang et al²³ that vaginal tape erosion/extrusion can occur at a late stage; surgeons need to be vigilant for this possibility. In our experience, we treat tape extrusion with excision of the eroded part as we don't find conservative treatment successful. Our results exclude possible asymptomatic tape erosions/extrusions.

QoL and sexual function can be quite complicated to assess at LT follow-up as many other confounding factors may have developed in participants' lives. The use of disease-specific questionnaires can help to overcome this issue to an extent. Similar to the E-TOT results at 1 and 3 years, clinically significant improvement in women's QoL was seen in the majority of women (76%) at median of 9-years follow-up. Our findings concur with Ulrich et al⁶ and Serrati et al⁷ who reported significant improvement in most QoL domains at 10-years follow-up following TO-TVT. The current evidence therefore tends to confirm that successful outcome of TO-TVT can have a long-lasting positive effect on women's QoL.

Only 87 women completed the sexual function questionnaire however this is the largest cohort assessing sexual function following TO-TVT at such long-term follow-up. The majority of women (61%) reported an improvement in sexual function however there is an apparent deterioration for one third of the participants. Several confounding factors may have occurred in that decade of follow-up that would inevitably impact women sexual function, such as advancing age, development of prolapse and menopausal vaginal dryness.

CONCLUSIONS:

This is the largest and longest follow-up RCT of TO-TVT. TO-TVT is associated with 71.6% patient-reported success rate, 4% groin pain/discomfort and 8% continence re-operation rate for TO-TVT at median of 9-years follow-up; the success rate is almost stable after 3-years.

Practical recommendations: Patients' can be counselled that the success rate for TO-TVT is almost stable after 3-years around 71% and the risk of chronic groin pain is 4% with 1.4% requiring medical or surgical treatment.

Research recommendations: Qualitative study is required to assess those participants with pain for severity; relation to the procedure; impact on QoL and any regret.

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FINANCIAL DISCLOSURES:

All conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending) are the following:

- Dr Abdel-Fattah has previously (none in the last 4 years) received fees for lectures and/or training courses for Bard, Coloplast, AMS, Pfizer and Astellas. University of Aberdeen

received research grant from Coloplast in 2009 to fund a study that I was the PI for. MAF is the previous chairman of the Scottish Pelvic Network; a network of clinicians, health professionals and academics in the field of pelvic floor disorders. SPFN received sponsorship for its annual meetings from various industrial companies.

- Dr. A. Mostafa received educational grant in 2012 from ICS Conference towards attending a medical conference
- Dr. D. Karmakar received educational grant in 2014 from Astellas towards attending a medical conference.

The ICMJE disclosure forms are available as online supporting information.

Author Contributions:

- Study concept and design: Abdel-fattah
- Acquisition of data: Karmakar;
- Data Analysis: Karmakar, Mostafa,
- Interpretation of data/ results: Karmakar, Mostafa, Abdel-fattah
- Drafting of the manuscript: Abdel-fattah, Mostafa, Karmakar
- Critical revision of the manuscript for important intellectual content: Abdel-fattah, Karmakar, Mostafa
- Obtaining funding: Abdel-fattah
- Administrative, technical, or material support: Karmakar, Mostafa
- Supervision: Abdel-fattah
- All authors had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis

ETHICAL CLEARANCE DETAILS:

The study timely received all required approvals from Research & Development Departments in Glasgow & Aberdeen and the relevant ethics committee WOSRES (Ref 05/S0702/6) and separate ethics approval was required and obtained in January 2014 for the long-term FU study.

The study was registered on www.clinicaltrials.gov (NCT00136071) in 2005.

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Table 1: Primary Outcome at 9 years follow-up

	Whole cohort	TOT (Outside-in)	TVT-O (Inside-out)	OR (95% CI)	p-value
PGI-I success♥	149/208 (71.63%)	76/104 (73.1%)	73/104 (70.2%)	0.867 (0.474,1.586)	0.760
Assume all missing data as failure	150/307 (48.9%)	77/151 (51.0%)	73/156 (46.8%)	0.85 (0.54,1.32)	0.534
Assume all missing data as success	249/307 (80.1%)	124/151 (82.1%)	125/156 (80.1%)	0.88(0.49, 1.56)	0.764
Last observation carried forward	223/307 (72.6%)	114/151 (75.5%)	109/156 (69.9%)	1.33 (0.80, 2.20)	0.288

♥Patient Global Impression of Improvement: Success defined as Very/Much Improved.

Table 2: Late Adverse Events

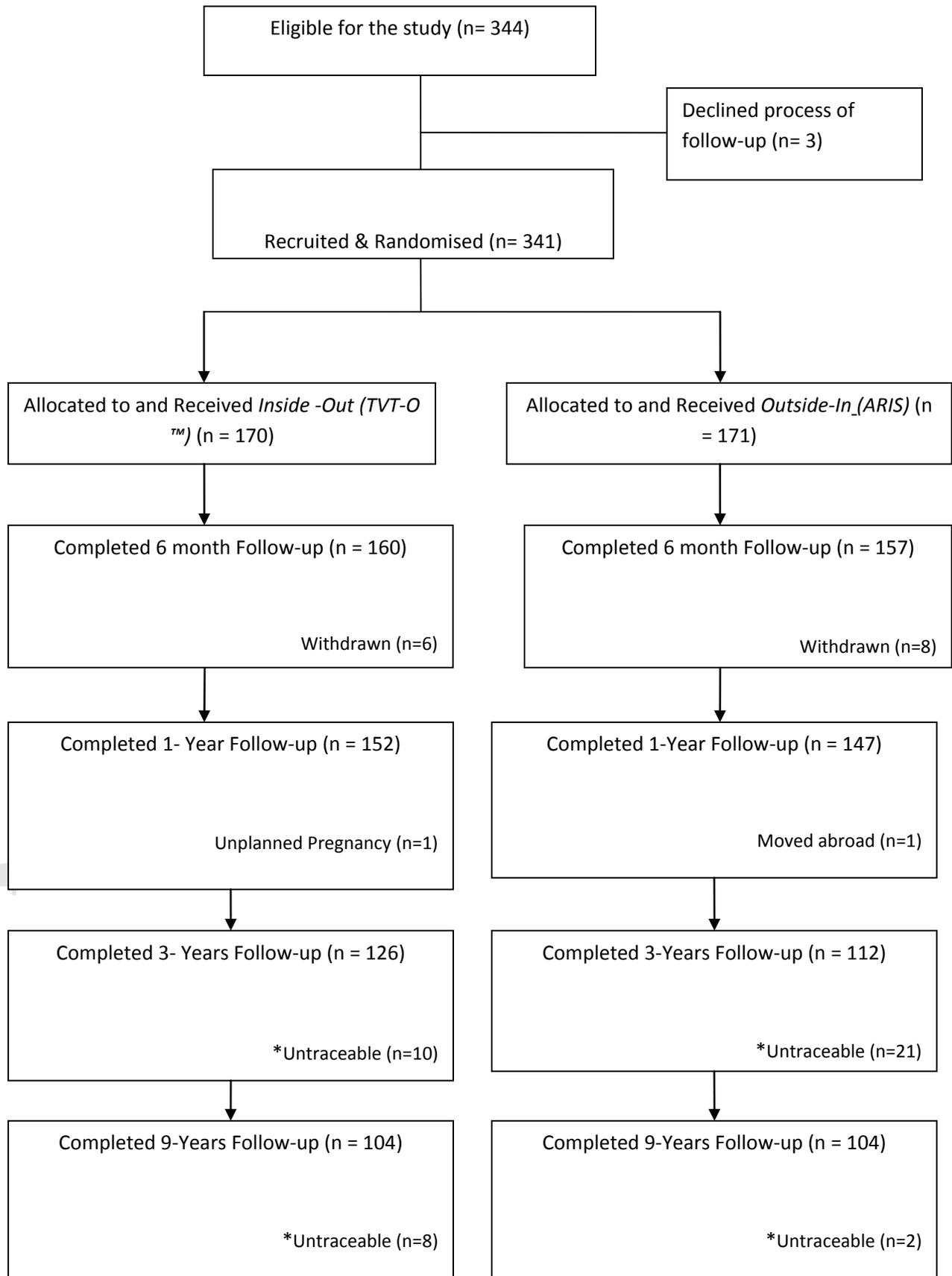
			TO-TVT Cohort (n=208) [†]		
De-Novo Urgency			(n=20) 9.61%		
CISC (Clean Intermittent Self Catheterisation)			(n=2) 0.96%		
Long-term Low-dose Antibiotics			(n=3) 1.44%		
Late Vaginal Extrusions			(n=4) 1.92%		
Any Groin/ Thigh/ Vaginal Pain*			(n=9) 4.32%		
Type of Tape	Age at 9 year FU	Further incontinence/ prolapse surgery within last 9 years	PGI-I Outcome	Pain Site	Treatment and Patients Comments
TOT	50	Repeat TVT-O	Success (Very Much Improved)	Not Specified	Pain-killers and antibiotics. Very Painful and always take infections down below.
TOT	55	NO	Success (Much Improved)	Back ache and Groin	Started in the last 6 month to have groin and back ache. No treatment*
TOT	54	NO	Failed (Much Worse)	Not Specified	Co-codamol-can't take Diazepam due to my Job and amitriptyline makes me sick
TOT	47	NO	Failed (Very Much Worse)	Not Specified	No treatment.*
TOT	62	NO	Failed (Same)	Groin & Thigh	Not sure if related, my doctor referred me to the hospital. No treatment*
TVT-O	55	NO	Success (Much Improved)	Back ache and Right Groin	No treatment*
TVT-O	65	Excision of Tape	Failed (Much Worse)	Not Specified	I had most of it removed for something growing over it – Take co-codamol for arthritis which helps.♣
TVT-O	48	NO	Failed (Improved)	Left Groin and left side of Stomach	IBS Worsened over last 4-years and will have hysterectomy. No treatment *
TVT-O	49	NO	Failed (Much Worse)	Not Specified	No treatment *

♣ On checking records; she had almost total excision of TVT-O (vaginal portion and up-to obturator muscle) due to erosion in lateral vaginal sulcus with growing granulation tissue on top and tenderness. She had a background of arthritis for which she was already on regular analgesia.

*Patients are not receiving any treatment for pain.

[†]AE were assessed among respondents only (n=208), as one single cohort.

Figure 1: Flow Chart of recruited patients & follow-up



*Postal questionnaires returned as in-correct address and correct address could not be established (e.g. patient moved address, moved abroad, etc)

*Participant failed to respond to follow-up questionnaires however her correct postal address was confirmed.

Figure 2A: Patient-reported success rate with TO-TVT over the period of follow-up

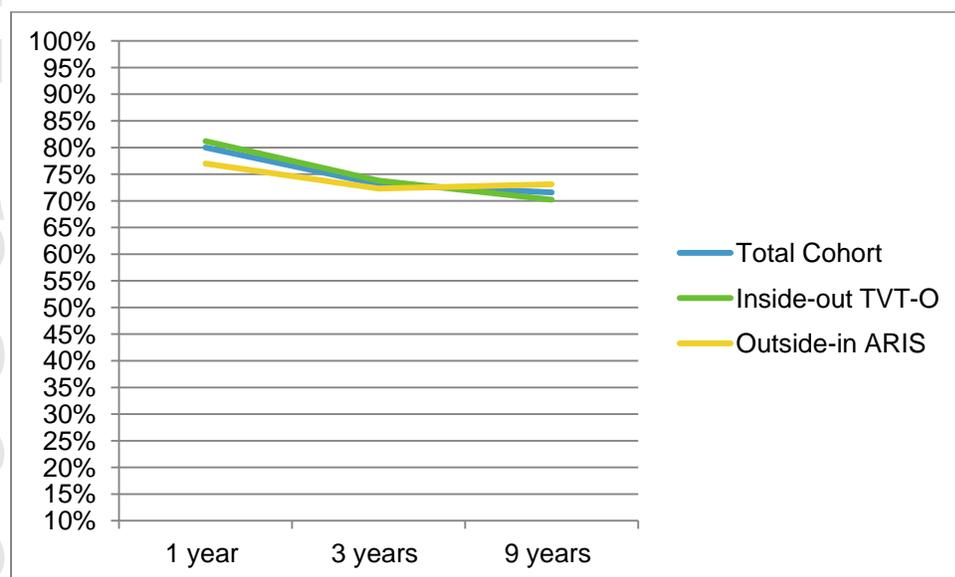


Figure 2 B: Cumulative Repeat Continence Surgery over the period of follow-up

