Intravenous versus subcutaneous drug administration. Which do patients prefer? A systematic review

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Abstract

Background Intravenous (IV) drug delivery is commonly used for its rapid administration and immediate drug effect. Most studies compare IV to subcutaneous (SC) delivery in terms of safety and efficacy but little is known about what patients prefer.

Methods A systematic review was conducted by searching 7 electronic databases for articles published up to February 2014. Included studies were randomised controlled trials (RCTs) or cross over designs investigating patient preference for SC versus IV administration. The risk of bias in the RCTs was determined using Cochrane Collaborations tool. Reviewers independently extracted data and assessed the risk of bias. Any discrepancies were resolved by consensus.

Results The search identified 115 publications, but few (6/115) met the inclusion criteria. Patient populations and drugs investigated were diverse. 4/6 studies demonstrated a clear patient preference for SC administration. Main factors associated with SC preference were time saving and the ability to have treatment at home. Only 3 studies used study-specific instruments to measure preference.

Conclusions Results suggest that SC is the patients' preferred route of drug delivery. Patient preference has clearly been neglected but it is important in medical decision making when choosing treatment methods as it has implications for adherence and quality of life. If the safety and efficacy of both administration routes are equivalent then the most important factor is patient preference. Future drug efficacy and safety studies should include patient preference and use adequate measures.

Key Points:

- Results suggest that the SC route is the patients preferred method of drug delivery
- Patient preference needs to be addressed in future RCTs. This is important when selecting methods of treatment as it has implications for adherence and quality of life

Introduction

Many drugs can be given in a variety of different ways, oral, parenteral, intravenous and subcutaneous. All have their potential advantages and disadvantages in terms of patients' convenience, pain, discomfort and impact on emotional and social well-being. If drugs have similar efficacy then patient preference for route of administration could be important and should support medical decision making. The various drug modalities, dosages and frequencies offer a wide option of choices to suit patients' needs and preferences. Consideration of such factors may help address the problem of treatment adherence especially in chronic medical conditions. Improvements in modern treatments have turned some diseases into chronic conditions (such as diabetes and cancer) so determining individual acceptability and choice of type of drug administration could enhance adherence to therapeutic regimens.

The intravenous (IV) and subcutaneous (SC) routes of administration have both benefits and drawbacks. IV delivery is advantageous as it allows an immediate effect of the drug to take place, the rate of distribution can be controlled, it assists those patients who cannot tolerate a drug orally or have swallowing difficulties, large doses can be infused expeditiously, and it permits continuous medication to be delivered [1]. Advantages of the SC route include the possibility of self-administration, greater mobility for patients, it provides an alternative for patients with poor venous access and can be administered at home, away from the hospital setting [2]. Cost is another element to take into account, and several studies have shown the cost effectiveness of SC delivery over the IV drug route [3-6]. In addition, out of pocket costs for patients and their families having to take time off work and travel to hospital for IV treatment could be underestimated.

There have been trials comparing IV and SC drug administration with most reporting on drug efficacy and safety [7-16]. In the study by Moreau et al (2011) [11], patients with relapsed multiple myeloma (MM) were randomised to receive bortezomib either by SC administration or IV infusion. Results revealed that the efficacy of SC bortezomib was non-inferior to IV administration. Adverse events were reported in 57% of patients in the SC group and 70% in the IV group, showing that SC has an improved safety profile. Because of these results the SC route of bortezomib was authorised for use within Europe [17]. Although the drug was approved, and fewer adverse events might lead to reasonable assumptions that patients would prefer SC delivery, these were not reported.

A recent study [16] has demonstrated that the pharmacokinetic profile of SC rituximab in patients with previously untreated follicular lymphoma was non-inferior to IV rituximab and was not associated with new safety concerns. IV infusions lasted 1.5 to 6 hours, whilst the median injection time for SC rituximab was 6 minutes, showing that SC delivery would improve convenience for the patient whilst decreasing the burden on healthcare costs. This study is currently investigating the views of the health care professionals regarding their preferred administration route, however it will not report on patient preference.

Some drugs are available in both IV and SC formulations permitting patients receiving long term treatment who can no longer tolerate IV therapy, to be given the drug subcutaneously, when for example repeated cannulation may have damaged peripheral veins. This is demonstrated in a study by Keystone et al (2012) [14]. Patients with rheumatoid arthritis who received at least four years of IV abatacept continued via the SC method. Safety, efficacy and immunogenicity was investigated and results showed that switching from IV to SC administration was well tolerated, had no increased safety concerns, no increased risk of immunogenicity and efficacy was maintained. These features paired with the fact that fewer than 10% of patients discontinued SC treatment suggests that patients may well prefer SC administration although the study did not investigate this formally.

There are in fact few studies where patients' preferences or acceptance for IV and SC drug administration are primary outcomes [18-24]. A good example is the report by Barbee et al (2013) [19] in which patients with MM who received at least one dose each of IV and SC bortezomib were asked via a questionnaire about their preference for route of drug delivery; 68% preferred SC whilst 25% favoured IV. However as with many other studies, this was not a randomised controlled trial (RCT). Such designs may affect outcomes because of the lack of random allocation to intervention groups that might have introduced bias [25].

A better understanding of patient preference is fundamental in assisting medical decision-making, particularly in patients with chronic health conditions where patients may be receiving treatment for long periods of time. In this systematic literature review, we investigated patient preferences for IV or SC drug administration which had been examined in RCTs or crossover designs.

Methods

Search strategy

A systematic, electronic search of AMED, CINAHL, MEDLINE, PsycINFO, PUBMED, SCOPUS and Science Direct was performed for articles published up until February 2014. A combined search was used including the terms 'preference', 'intravenous vs. subcutaneous' OR 'intravenous versus subcutaneous' in the various databases. No restrictions regarding the time period or the type of study were applied during the initial search. A hand search was conducted on the relevant papers retrieved, to examine additional related studies.

Selection Criteria

All duplicates were excluded from the initial computerised search. Only publications of studies that met the following criteria were included: (1) comparison of SC with IV drug administration, (2) investigation of patients' preferences for SC and IV drug administration, (3) either a RCT or cross-over study design, (4) original full reports (i.e. conference abstracts or posters, reviews, meta-analyses, and commentaries were excluded) and (5) adults over 18yrs. In the first selection stage

titles, abstracts and information on the studies were screened to assess whether they were original full reports. In the second stage, abstracts and/or full copies of the articles were reviewed for final selection by two reviewers (KS and HH), followed by the hand search.

Methodological quality assessment

The methodological quality of each article was assessed using the Cochrane Collaboration's tool for assessing risk of bias, which rates the quality of RCTs [26]. The original version of the tool consists of seven items that are used to assess the risk of bias in the RCTs. However for this systematic review the item 'blinding of participants and personnel' was removed due to the nature of the intervention (it is not feasible to mask for treatment allocation). This resulted in a six-item scoring system using random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. A judgement of risk of bias was assigned to each scoring item (1=low bias, 0=high bias or unclear bias,) and a total risk of bias score was calculated. Each trial was then assigned a quality rating based on the number of low risk judgements ranging from good quality (total score 5-6), fair quality (3-4) to poor quality (0-2). Two reviewers (KS and HH) independently assessed the methodological quality of the included studies. Any differences in rating and/or discrepancies were resolved following discussion.

Results

Search Results

The search produced 151 hits (Figure 1) from 1974 to February 2014. Duplicates were excluded, leaving 115 potentially relevant studies. The titles, abstracts and information of these citations were screened for relevance to the review topic, leaving 34 studies to be assessed further. The abstracts and/or full texts of the 34 studies were retrieved, evaluated in detail and filtered according to the eligibility criteria. After this stage five studies were left for inclusion in the review [27-31]. A hand search of the references of relevant citations resulted in an additional study being included in the final review [32]. In total, 6 studies met the selection criteria and details are summarised in Table 1.

Four of the RCTs used a crossover design. A total of 410 participants were evaluated across the six studies. The sample sizes ranged from 9-248 participants at baseline. The age range of participants (taken from five studies that adequately reported the age range) was 18-85 years. The samples across the six studies predominantly focused on females (83% female, 17% male). The study population were diverse. Studies included participants with cancer, Crohn's disease (CD), primary antibody deficiencies, multifocal motor neuropathy (MMN), primary invasive breast adenocarcinoma, deep vein thrombosis (DVT) and patients scheduled for elective abdominal or extremity surgery.

Study quality

Three of the studies were of good methodological design with low risk of bias (see Table 1). The remaining three studies were of fair methodological quality. In the studies of a fair methodological quality, possible areas of bias were reported in 'random sequence generation' and 'allocation concealment'. In general the studies seemed sound however the possibility of bias was raised due to under-reporting, particularly in earlier publications. All studies showed a low risk of bias on the 'incomplete outcome data'.

Patient preferences

The majority (4/6) of the studies concluded that patients had demonstrated a preference for SC drug administration [27-30] proportions ranged from 44%-91%. Only one study reported that patients preferred IV drug delivery [32] and another found no difference in patient preference for either method [31].

Assche et al (2012) [28] investigated elective switching between anti-tumour necrosis factor agents in patients with CD. The 73 patients either continued receiving IV infliximab (IFX), or switched to SC adalimumab (ADA) administered every other week. Patient preference was investigated in the ADA arm with a study-specific questionnaire. SC ADA was preferred by patients at the majority of time points (6/7) throughout the trial but reasons for preference were not reported.

The study by Harbo et al (2009) [29] was conducted on patients with MMN. Patients were randomised to either receive SC or IV immunoglobulin (Ig) of equal doses. The first therapy was given for a period of 18-56 days. Patients then crossed over to receive the alternative treatment. IV treatment was given in the hospital. During a hospital stay a nurse taught patients how to self-administer SC Ig, allowing treatment to be administered at home. Patients gave a detailed description of their preference (method unknown). 44% (4/9) of patients had a predilection towards SC Ig, 22% (2/9) favoured IV administration and 33% (3/9) gave no preference. Reasons given by patients for SC Ig preference were that treatment could be given at home and it allowed them to avoid difficulties with IV access. However, patients reported that the increased number in treatment days was a disadvantage for SC Ig.

Pivot et al (2013) [30] investigated the preferences of women with HER2-positive breast cancer for SC or IV trastuzumab. Patients were randomised to receive either four cycles of SC or IV trastuzumab and then crossed over to receive the alternative method of treatment. Two study-specific interviews gathered patient choices and reasons for preferred treatment; one was conducted at baseline, the other after the cross over period. 96% (112/117) patients who received SC trastuzumab first, favoured the SC route of administration whereas 4% (5/117) chose the IV route. In patients who received the IV route first, 87% (104/119) preferred SC, 9% (11/119) favoured IV delivery and 2% (4/119) had no preference. Overall 92% (216/236) of patients preferred SC and 7% (16/236) IV trastuzumab, 2% (4/236) had no preference. In 74% (159/216) of patients, the preference for SC was 'very strong', 'fairly strong' in 21% (45/216) and 'not very strong' in 6% (12/216). Preference for IV

route was ‘very strong’ in 50% (8/16) of patients, ‘fairly strong’ in 19% (3/16) and ‘not very strong’ in 31% (5/16). Reasons for choosing SC were primarily time saving in 90% (195/216) of patients, less pain/discomfort in 41% (88/216), patient convenience in 16% (35/216), easier administration in 15% (33/216), problems with IV administration in 12% (25/216) and less stress and anxiety in 7% (15/216). One of the main reasons for the 16 patients preferring the IV route were that 69% (11/16) patients had fewer reactions (less pain, bruising irritation etc.) to that method.

Robinson’s et al study (1993) [27] focused on patients with DVT. Patients were randomised to receive calcium heparin SC or sodium heparin given IV. Patients then crossed over to receive the alternative treatment. At the end of the study patients were questioned on their overall partiality for form of treatment (method unknown). 79% (15/19) of patients favoured the SC route. 11% (2/19) chose the IV route and 11% (2/19) gave no preference. Patients reported significantly less discomfort felt at the SC injection site ($p<0.001$). Patients also perceived that their mobility was better during the last days of treatment when they were receiving SC heparin ($p<0.005$).

In contrast Chapel’s et al (2000) [32] study on patients with primary antibody deficiencies found that patients preferred IV method of drug administration. Patients received either SC or IV Ig therapy for one year and then received the alternative treatment for an additional year. At the end of the study patients were asked which method they preferred (methods not reported). Results showed that 62% (16/26) patients favoured IV application compared with 38% (10/26) patients who preferred the SC route. Four patients had no preference. Reasons for preference were not reported.

The study by Urquhart et al (1988) [31] assessed patient controlled analgesia (PCA) in patients undergoing elective abdominal or extremity surgery. Patients were randomised to receive either SC or IV PCA. When patients reported pain, hydromorphone was administered until they no longer experienced any discomfort. A PCA infuser was then attached to the patient, allowing patients to self-administer hydromorphone either IV or SC for the duration of their stay in the hospital. After completion of PCA therapy patients were asked about their overall satisfaction with the technique via a study-specific questionnaire. 80% (12/15) patients in the SC group rated their pain control as excellent, as did 67% (10/15) patients in the IV group. However there were no differences in the patients’ ratings of overall satisfaction in their analgesic therapy between both treatment groups.

Quality of life (QoL)

Two studies also reported on patients’ QoL in addition to preference. In the study by Harbo et al 2009 [29], patients completed the generic SF-36 questionnaire [33]. The hypothesis was that QoL would improve in patients with MMN following SC delivery of Ig, as this could be given at home. Although SC administration was the route that was preferred by most of the patients in the study, no significant differences in the QoL scores were found.

Assche et al 2012 [28] used the disease-specific IBD questionnaire to measure QoL [34]. This enquired about general preference, the benefit from therapy, mode of administration, impact on

activities of daily life, burden of adverse events and financial implications. Patients had a predilection for SC over IV on all aspects of QoL apart from the financial impact of treatment.

Efficacy and safety

Although the focus of this review is on patient preferences, the primary outcome in 4/6 studies [27, 29, 31, 32] was to evaluate the the non-inferiority of SC to IV drug delivery, and all demonstrated comparable efficacy and safety profiles of the two methods of drug administration. The two studies [28, 30] that included patient preference in the primary study outcomes showed more diverse results regarding efficacy and safety. Pivot et al (2013) [30] concluded that SC trastuzumab is a valid treatment alternative because it has a similar safety profile as well as a pharmacokinetic profile and efficacy that is non-inferior to IV administration. In contrast, Assche et al (2013) [28] reported treatment termination because of a loss of tolerance in 10/36 patients receiving SC ADA compared to only 1 patient in the IV drug administration arm. A loss of efficacy was shown in 4/36 patients receiving SC ADA, however despite this patients still reported a preference for SC administration.

Discussion

The present review evaluated patients' preferences within RCTs for either SC or IV drug administration. An extensive literature search revealed six RCTs [27-32]. Despite the heterogeneity of the studies, overall findings demonstrate clear patient preference ranging from 44% [29] to 91% [30] for the SC route. Factors associated with SC preference were that patients were able to have the treatment at home [29], saved time (e.g. travel time to the hospital) [29], avoided problems with IV administration or vein access [29, 30], and reduced discomfort [27].

The studies included in this review not only showed diversity regarding patient population and the drugs investigated, but also in the period of time that the drugs were administrated. Treatment time ranged from two days in a PCA trial [31] to 2 years in a trial examining Ig replacement therapy in patients with primary antibody deficiencies [32]. This is important to take into account as patient preference for administration route may differ according to the length of time patients spend receiving the drug. For example, patients who require long-term drug treatment may experience damage to their veins, which no longer allows them to tolerate IV delivery. These patients may welcome SC administration, whereas those who are given drugs for a shorter duration or in a one-off-treatment may not be affected and therefore show little or no preference for mode of drug delivery. Our review confirmed that an increase in the length of required treatment was associated with preference for SC administration [28-30].

The outcome measures addressing patient preference varied between studies. Half of the studies lacked a description of study measures, resulting in a possible bias or problems regarding the validity of the results [27, 29, 32]. The three remaining studies used study-specific instruments either

questionnaires or field tested-interviews [28, 30, 31]. However, the fact that all measures were study-specific highlights that patient preference is often overlooked in most drug administration trials as there are no validated instruments available.

A strength of the current review is that only RCTs were included. Although there are other good quality studies that examine patients' preferences [18-24], none are RCTs. For example, one study measured preferences of IBD patients for two anti-TNF agents in terms of their mode of administration by using hypothetical scenarios [18]. However, until patients actually have the drugs administered and experience the different modes of delivery, the route they favour may differ.

Our review has few limitations. One of these is the appraisal system we used [26]. This particular method focused on whether or not the study had properly been set up as an RCT to eliminate bias, rather than an in depth appraisal that may have been achieved by using another process. In addition, as blinding for treatment allocation was not possible in most studies - only one study was single-blinded [29], part of this tool could not be used.

As far as we are aware this is the first review focusing on patients' preferences for either IV or SC administration. One other review compared different aspects of SC and IV routes (including health related QoL, treatment satisfaction and convenience) but only included studies in patients with primary or secondary antibody deficiencies [35].

A partiality by patients for administration route is an important issue that needs more consideration especially as time is a very precious commodity for patients with life-threatening and/or chronic disease. The extra survival time achieved through efficacious drugs needs to be balanced against the efforts and burdens required to have the treatment administered. Both the lack of literature and the fact that only one study assessed patient preference as the primary outcome measure [30] demonstrate how this area is neglected. This evidence establishes that patients are not given the chance to decide which medical treatment is most beneficial to them. Patient preference is one of the most significant factors in treatment-related decision making and could possibly affect patient's QoL and treatment compliance.

Addressing patient preferences in future research is vital in regards to medical decision making. Future studies should include an RCT or crossover design and incorporate health-related QoL. There is also scope for some standardisation in the methodology employed to measure preferences as this would increase the validity within the research. If the safety and efficacy of the two methods is proven to be non-inferior to one another, patients should have a choice in what route they receive, based on what is beneficial to them. This is particularly the case for individuals who undergo long-term treatment for chronic diseases.

Conflict of interest

The authors of the review have no conflicts of interest to declare.

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Table 1. Studies included in the final review

Author, year & country	Aims of study	Sample	Procedure	Outcomes	Results	Appraisal/quality assessment
Assche et al. 2012, Belgium single-centre [28]	To evaluate prospectively the impact of elective switching of patients with CD with IV IFX to SC ADA and to assess patient preference	*N*=73. Median age 38 in ADA group and 37 in IFX group. Age range 27-47 years.	Patients received scheduled IFX maintenance for ≥ 6 months before study participation. They were then randomised to either continue IV IFX (n=37) or switch to SC ADA (n=36) for 56 weeks	Diary-based CDAI assessed disease activity. IBDQ measured QOL. Study-specific questionnaire assessed general preference at different time points. Patient preference only assessed in SC ADA patients	Significantly more patients preferred SC over IV (p=0.8 at 56 weeks/end of study.) Clear preference (% not reported) for SC administered therapy for most items on study-specific questionnaire except financial impact of treatment	Good quality 5/6 low risk of bias
Chapel et al. 2000, , International, multi-centre [32]	To compare the efficacy of IV versus SC Ig replacement	*N*=30. Mean age 44 years. 20 female, 10 male.	Crossover, Cross-overdesign. Patients	Number, length and severity of infections was	22 completed study (2 years of treatment); 8 withdrew, 4	Fair quality 3/6 low risk of bias

	therapy to prevent infections in patients with primary ADSs, and to assess patient preference for administration route		randomised to receive SC or IV therapy for 1 year and then switched to alternative treatment for 1 year	measured during treatment periods. Days lost from school/ work due to infections recorded. Patient preference gathered at completion of study; methods unknown	completed one phase. 16preferred IV and 10 preferred SC; 4 had no preference	
Harbo et al. 2009, Denmark. multi-centre [29]	To investigate in patients with MMN, whether self-infusions of SC Ig are as effective, feasible and safe as an IV infusion, and	*N*=9. Mean age 49 years. 5 female, 4 male. All patients had IV Ig maintenance therapy prior to study inclusion	Cross-over design. Patients randomised to receive SC Ig or IV Ig for 18-56 days, followed by either IV or SC	SF-36 questionnaire assessed HRQOL. Patients described their preference for therapy; methods unknown.	45% (4/9) preferred SC due to no end of dose weakening, treatment at home, avoidance difficulties IV access. 22%	Good quality 6/6 low risk of bias

	whether SC self-infusions at home are associated with better QOL in comparison to IV administration.		respectively		(2/9) preferred IV because of avoidance of treatments several times per week. 33% (3/9) had no preference. No significant differences in QOL scores during SC and IV administration period	
Pivot et al. 2013,International, multi-centre [30]	To assess patient preference for SC or IV trastuzumab in the adjuvant breast cancer setting	*N*=248 women with HER2-positive primary invasive breast adenocarcinoma. Median age 53 years. Patients were either trastuzumab naïve or had	Cross-over design. Patients were randomised to receive 4 cycles of SC or IV trastuzumab, and then crossed over	Two study specific telephone interviews assessed preferences and strength of preferences.	236 patients were included in intention-to-treat population. 91% (216/236) patients preferred SC (*P*<0.0001).	Good quality 6/6 low risk of bias

		already received IV trastuzumab as part of treatment	to receive the other method of trastuzumab administration for 4 cycles.		7% (16/236) preferred IV and 2% (4/236) had no preference. Preference of SC was very strong in 67% (159/236)	
Robinson et al. 1993, UK, single-centre [27]	To assess and compare patient acceptability and preferences for SC versus IV heparin in the treatment of DVT	*N*=20. Mean age 55 years. 7 male, 13 female.	Cross-overdesign. Patients received either IV or SC heparin for 3 days, and then crossed over to receive the other method of heparin administration for 3 days.	VAS assessed acceptability of administration methods for discomfort in affected leg, pain at injection site, and mobility. Patients' preference for method of administration was gathered at completion of study;	78% (15/19) preferred SC (*P*<0.001). 11% (2/19) preferred IV and 11% (2/19) gave no preference. Less discomfort at injection site with SC administration (p<.001)	Fair quality 3/6 low risk of bias

				methods unknown.		
Urquhart et al. 1988, USA single-centre [31]	To compare the efficacy of SC PCA to IV PCA in patients scheduled for elective abdominal or extremity surgery	*N*=30. Mean age 52 years in IV group, 44 years in SC group. 12 male, 18 female.	Patients received either IV (n=15) or SC PCA (n=15).	5-point scale assessed postoperative analgesia at 4-hr intervals. Study specific questionnaire assessed self-reported incidence of side effects and overall satisfaction with route of administration.	No difference between groups in self-reported incidence of side effects or satisfaction with route of administration	Fair quality 3/6 low risk of bias

ADA Adalimumab, ADS Antibody Deficiency Syndrome*, CD* Crohn's Disease, *CDAI* Crohn's Disease Activity Index, *DVT* Deep Vein Thrombosis, *HRQOL* Health Related Quality of Life, *HER2* Human Epidermal Factor Receptor Type 2, *Ig* Immunoglobulin, *IBDQ* Inflammatory Bowel Disease Questionnaire, *IFX* Infliximab, *IV* Intravenous, *MMN* Multifocal Motor Neuropathy, *PCA* Patient Controlled Analgesia, *QOL* Quality of Life, *RCT* Randomised Controlled Trial, *SF-36* Short Form 36 Item Questionnaire, *SC* Subcutaneous, *VAS* Visual Analogue Scale

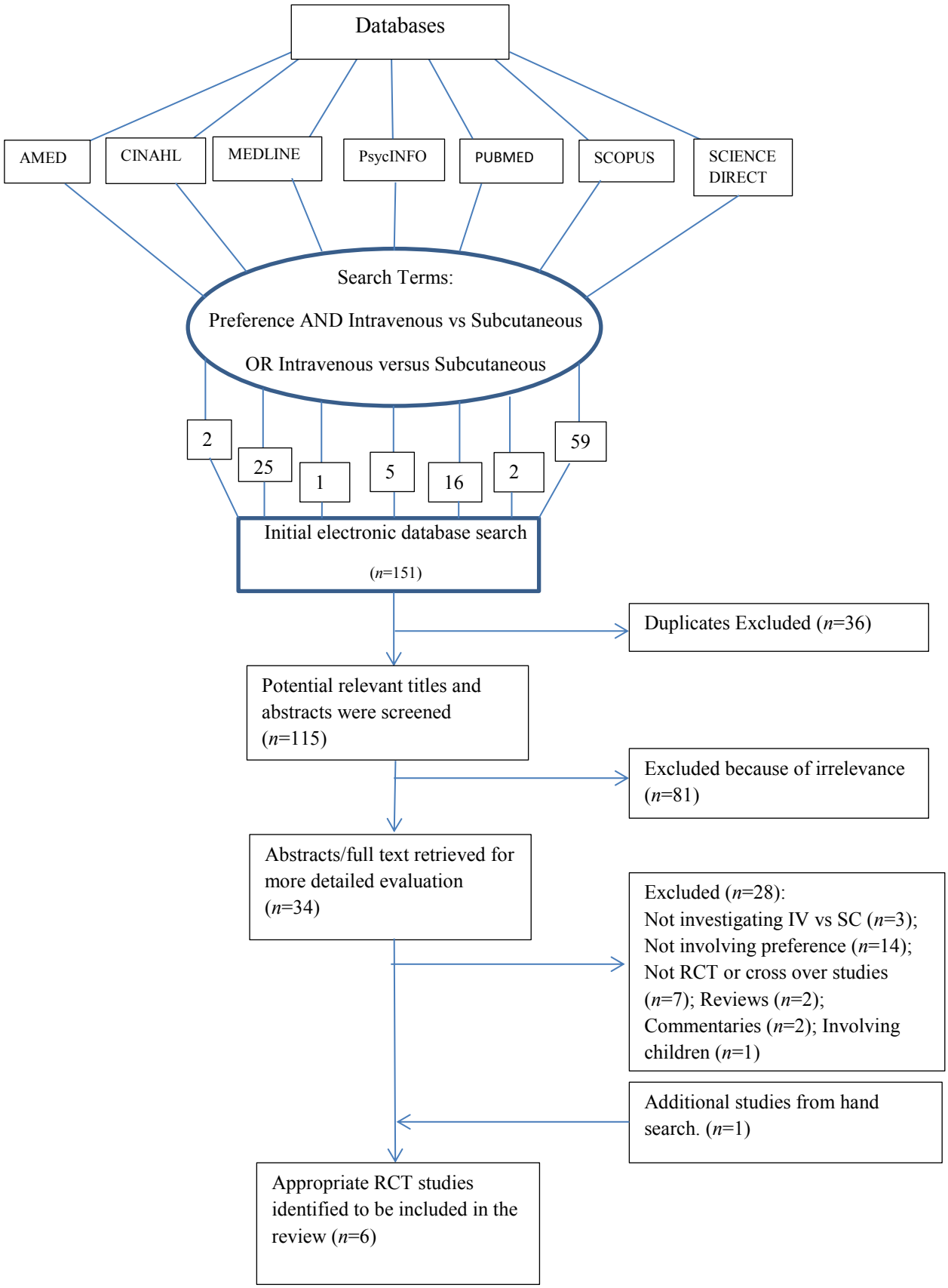

Fig.1 Search Results