Patient Preference and Adherence

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ORIGINAL RESEARCH

Patient Experience and Improvement Opportunities in Self-Administered, Large-Volume Subcutaneous Infusions at Home

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Purpose: Subcutaneous (SC) administration is largely established as the preferred route to deliver biotherapeutics. Although the majority of approved SC products are limited to dose volumes ≤2.25 mL, there has been increasing industry focus on large-volume SC (LVSC) development. To date, however, there are few LVSC biotherapeutics available for self-administration, and subcutaneous immunoglobulin (SCIg) remains the most established example. As a result, there is limited published literature on real-world practices with LVSC therapies to inform user needs and preferences for delivery device design attributes.

Patients and Methods: This was a remote ethnography study of patients self-administering SCIg at home for treatment of primary immunodeficiency diseases (PIDD). Participants passively video recorded their preparation and infusion processes, took photos, and provided open responses to illustrate their overall experiences with their disease, infusions, and delivery devices. Qualitative data were compiled, analyzed, and grouped into themes and subthemes that represented participant responses and sentiments.

Results: A total of 11 patients completed the remote study, all of whom were diagnosed with PIDD. Enrolled participants were currently infusing SCIg with one of five delivery devices and most also had previous experience with another delivery device. Emerging themes included universal preference for SC administration and pain points associated with managing medication/supply orders, storing medications/supplies, troubleshooting device issues, performing burdensome medication preparations, priming tubing/needles, inserting/securing needles, programming devices, adapting to device volume constraints, and loading reservoirs or tubing into delivery devices.

Conclusion: Although patients prefer LVSC administration at home compared to the alternatives, the current SCIg use process presents a variety of challenges. While not all of these factors will apply to every LVSC scenario, these insights, along with their corresponding implications for device design, provide a framework to inform user needs for LVSC self-administration, anticipate obstacles during development of new LVSC therapies, and improve existing delivery devices.

Keywords: large-volume subcutaneous drug delivery, self-administration, drug delivery devices, home infusion, primary immunodeficiency diseases, subcutaneous immunoglobulin

Introduction

Intravenous (IV) administration has historically been the standard of care to deliver many biotherapeutics, including monoclonal antibodies (mAbs).[1] Despite efficacy and predictable bioavailability, IV delivery has practical limitations in that it requires invasive access, healthcare professional (HCP) services, potentially complex administration procedures, and typically travel to a healthcare facility, all of which can burden patients and the healthcare system.[2–8] To address these constraints, subcutaneous (SC) administration has emerged as the preferred route to deliver biotherapeutics, as it offers numerous and well-established benefits compared to IV administration.[9] For HCPs and the broader healthcare system, these include increased operational efficiency and decreased overall treatment costs.[10,11] For patients, they include reduced treatment burden, decreased infusion-related adverse effects, increased convenience, and improved quality of life.[12–14] Although not exclusively, many of these patient-centered benefits can be attributed to the ability to self-administer SC treatments outside of traditional healthcare settings, namely at home.

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In order to help facilitate at-home administration, a variety of delivery systems, including prefilled syringe (PFS), autoinjector (AI), on-body injector (OBI), and portable infusion pump (PIP) devices have evolved alongside SC biotherapeutic development.[15,16] This device innovation has resulted in the approval of over sixty biologic-device combination products,[17] where the medication and delivery device are intrinsically linked, and 510(k) clearance of several general-purpose PIP devices for biotherapeutic delivery.[18,19] Despite clear progress, SC delivery of larger dose volumes (ie, >3 mL) has presented well-known and intertwined formulation, clinical development, and device challenges, including protein stability concerns at high concentrations, formulation viscosity constraints, potential pharmacokinetic bridging complexities, and lack of timely device availability for pivotal trials.[20–25] Amid these challenges, the vast majority of approved SC products are still limited to dose volumes ≤2.25 mL.[17] However, the recent IV-to-SC transition of mAbs used to treat cancer has particularly accelerated focus on large-volume SC (LVSC) development, as these products often require comparably higher doses to achieve their therapeutic effects.[25] While all approved SC oncology mAbs are currently supplied in conventional vials to be prepared and administered by HCPs in healthcare settings,[26–30] at-home and self-administration is being actively explored,[31–40] which may inevitably increase the demand for more patient-centric delivery devices.[41]

To date, however, there are very few LVSC therapies available for self-administration that have dose volumes similar to those of SC oncology mAbs, which are on the order of 5–15 mL for approved products.[23] Four biotherapeutics have been approved for delivery via OBI[42–45] with other devices in development,[20] although one product was recently withdrawn from the market,[46] another will seemingly be discontinued,[47] and not all can achieve these dose volumes with a single device. The most established LVSC example is subcutaneous immunoglobulin (SCIg), a purified immune globulin derived from pooled human plasma that is the mainstay of treatment for primary immunodeficiency diseases (PIDD) and other diseases affecting the humoral immune system.[48] A variety of SCIg products are available that vary in formulation concentration and composition, packaging configuration, recommended infusion volumes and rates, pharmacokinetic profiles, and typical dosing frequencies.[49] Table 1 provides a brief overview of SCIg products available in the US market with their relevant administration-related characteristics, adapted from a recent and comprehensive review by Mathias et al[50] and supplemented with additional information from product labeling.[51–56] Regardless of the product selected, SCIg treatment decisions such as dose, dosing frequency, administration method and equipment, number of infusion sites, and infusion parameters are highly individualized to each patient based on a combination of pharmacokinetic monitoring (ie, immune globulin trough levels), clinical response (ie, frequency of infections), tolerability, and preference.[48]

As no biologic-device combination products currently exist for SCIg, available treatments are administered using one of several general-purpose PIP devices.[57] Each of these devices has a corresponding set of supplies and accessories that are intended to be used with their respective PIP.[58–60] Table 2 summarizes key attributes of a subset of commonly used PIP systems, including device features and associated supplies according to product labeling.[61–65] With one exception, SCIg products are supplied in vials and require patient manipulation steps prior to administration, which may include withdrawing dose volumes into conventional (eg, polypropylene) syringes, pooling multiple vials, and "nose-to-nose" transfer to appropriate syringes for loading into PIPs.[66] Depending on the delivery method, additional administration-related steps may include inserting and securing needles, priming infusion sets, programming PIPs, initiating/manually administering infusions, and disposing of supplies.[67] Ancillary supplies, such as syringes, needles, vial adaptors or transfer spikes, tubing sets, pooling bags, alcohol wipes, tape or bandages, gloves, and sharps containers are typically provided by the dispensing pharmacy or home infusion provider to facilitate patient preparation and administration.[49] Still, current guidelines stress that providers must be able to offer adequate education, training, and support for patients to ensure they have the necessary tools and guidance to prepare and self-administer SCIg.[48]

Although SCIg is a cornerstone treatment, its use is still comparatively rare, given that the estimated prevalence of PIDD is between 1 in 1000 and 1 in 5000.[68,69] As a result, while studies have evaluated some elements of the SCIg use process such as treatment preferences,[70–72] packaging configurations,[66] administration methods,[73–77] training impacts,[78] treatment burden,[79,80] and overall lived experience with PIDD,[81–83] to our knowledge, no study has specifically explored real-world practices with self-administered SCIg or other LVSC therapies through a delivery device lens. Clear gaps in this area have been reinforced by a recent systematic survey conducted by the Subcutaneous Drug Development & Delivery Consortium that centered on high-dose/high-volume SC technology development and patient preference for SC

Table 1 Overview of SCIg Products Available in the US Market

SCIg Class	Product	Product Configuration(s) with Grams of Ig/mL	Recommended Max Volume Per Site	Recommended Max Infusion Rate Per Site	Recommended Max Number of Simultaneous Sites	Priming Specifications	Device/Administration Specifications
cSCIg	Cutaquig® (16.5% IgG)	Vial: 1 g/6 mL, 1.65 g/10 mL, 2 g/12 mL, 3.3 g/20 mL, 4 g/24 mL, 8 g/48 mL	40 mL	52 mL/hr/site	6	Prime manually (ie, not with the pump) and stop priming before fluid reaches the needle tip.	Follow pump manufacturer's instructions to prepare the pump and start the infusion.
	Cuvitru® (20% IgG)	Vial: 1 g/5 mL, 2 g/10 mL, 4 g/20 mL, 8 g/40 mL, 10 g/50 mL	60 mL	60 mL/hr/site	4	Prime manually (ie, not with the pump) up to the needle hub.	Follow pump manufacturer's instructions to prepare the pump and start the infusion.
	Gammagard Liquid® (10% IgG)	Vial: 1 g/10 mL, 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL, 30 g/300 mL	30 mL	30 mL/hr/site	8	Prime manually (ie, not with the pump) if using a syringe driver pump. Prime tubing up to the needle hub to ensure that no air is left in the tubing and needle.	Follow pump manufacturer's instructions to prepare the pump and start the infusion.
	Hizentra® (20% IgG)	Vial: 1 g/5 mL, 2 g/10 mL, 4 g/20 mL, 10 g/50 mL PFS: 1 g/5 mL, 2 g/10 mL, 4 g/20 mL, 10 g/50 mL	25 mL*	25 mL/hr/site*	8	Prime manually (ie, not with the pump) and stop priming before fluid reaches the needle.	An additional adapter may be required for PFS to fit properly in the infusion pump. Follow pump manufacturer's instructions to prepare the pump and start the infusion.
	Xembify® (20% IgG)	Vial: 1 g/5 mL, 2 g/10 mL, 4 g/20 mL, 10 g/50 mL	25 mL	35 mL/hr/site	6	Prime manually (ie, not with the pump) until a drop of fluid comes out of the needle.	Follow pump manufacturer's instructions to prepare the pump and start the infusion.
fSCIg	HyQvia® (10% IgG + rHuPH20)	Vial: 2.5 g/25 mL, 5 g/50 mL, 10 g/100 mL, 20 g/200 mL, 30 g/300 mL	600 mL†	300 mL/hr/site	2†	Prime either manually or with the pump up to the needle hub	Follow pump manufacturer's instructions to prepare the pump and start the infusion. Pump must be able to infuse at a rate up to 300 mL/hr/site, titrate flow up and down, and have a maximum occlusion alarm of at least 11.6 psi.

Notes: The above reflects parameters for a typical adult patient on maintenance therapy for treatment of primary immunodeficiency diseases. For some products, parameters vary for initial infusions and/or start of infusions, other indications (eg, chronic inflammatory demyelinating polyneuropathy), pediatric/adolescent patients, or those with lower body weights. *Maximum infusion volume and rate for treatment of chronic inflammatory demyelinating polyneuropathy are 50 mL/site and 50 mL/hr/site, respectively. †Maximum infusion volume and number of sites for treatment of chronic inflammatory demyelinating polyneuropathy are 400 mL/site (if 3 sites are used) and 3 sites, respectively.

Abbreviations: cSCIg, conventional SCIg; fSICg, facilitated SCIg; PFS, prefilled syringe; IgG, immunoglobulin G; rHuPH20, recombinant human hyaluronidase.

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Table 2 Attributes and Supplies of Commonly Used PIP Devices

PIP Type	PIP Device	Manufacturer	Drive Mechanism	Programming	Flow Control	Flowrate Accuracy	Compatible Reservoir(s)	Compatible Tubing/Needle Set(s)
Syringe driver	Freedom60®	KORU Medical Systems	Purely mechanical, spring-based	None	Dictated by flow restriction	±15% nominal	Becton Dickinson Luer-Lok 50 mL, Medline 60 mL luer-lock, Hizentra 50 mL PFS	Precision™ Flow Rate Tubing, High-Flo Subcutaneous Safety Needle Sets™, Low Residual Volume Y-Connector, and Extension Set (KORU Medical Systems)
	FreedomEdge®						Becton Dickinson Luer-Lok 20 or 30 mL, Hizentra 20 mL PFS	
	SCIg60™	EMED Technologies	Purely mechanical, spring-based	None	Dictated by flow restriction	±15% nominal	Becton Dickinson Luer-Lok 50 mL, Hizentra 50 mL PFS	Infuset™, VersaRate®, or VersaRate® Plus flow controllers (EMED Technologies) SUB-Q, SAF-Q®, or OPTFlow™ needle sets (EMED Technologies)
	Crono S-PID 50	CANÈ SpA	Electromechanical, piston-based	Time or flow rate modes	Dictated by pump programming	±3% nominal	Dedicated 50 mL luer-lock syringe (CANÈ SpA)	No dedicated tubing/needle set; Soft-Glide™ (EMED Technologies) and neria™ (Convatec) listed on product website
Peristaltic	CURLIN® 6000	Moog Medical	Electromechanical, curvilinear peristaltic finger action	Five different delivery modes	Dictated by pump programming	±5% nominal	Not specified	CURLIN® infusion administration sets (Moog Medical) Compatible needle sets are not specified
	CADD-Solis VIP™	ICU Medical	Electromechanical, linear peristaltic with active inlet and outlet valves	Five different delivery modes	Dictated by pump programming	±6% nominal	CADD medication cassette reservoirs (ICU Medical)	CADD extension sets, CADD administration sets, CADD high volume administration sets

Notes: The above is a representative list of commonly used PIP devices and is not intended to be exhaustive.
Abbreviations: PFS, prefilled syringe; PIP, portable infusion pump.

design attributes.[84] Briefly, 20 subject matter experts currently working in/on developing SC-administered products were asked to rank the importance of 33 parameters in terms of their impact on patient experience around the SC drug development/delivery process and the need for additional data/knowledge surrounding each parameter. The authors found that despite being ranked as the *most important* factors by the subject matter experts for impact on patient experience, the parameters "complexity of user steps", "form factor/human factors considerations", and "number of use steps to administer dose" were identified among those with the *largest data gaps*.

To help address these and related knowledge gaps, we conducted a remote ethnography study specifically designed to characterize the full patient use process with SCIg, including treatment decisions, medication procurement, storage, preparation, and administration with various delivery devices. The primary goals of this study were to: (1) document real-world practices and challenges experienced by patients self-administering SCIg at home, with particular focus on the use of delivery devices; (2) identify opportunities to improve the current use process through qualitative thematic analysis; and (3) inform user needs for future devices designed to deliver SCIg and LVSC treatments more broadly as this landscape expands to other disease areas.

Materials and Methods

Study Design

This was a US-based, mixed-methods, semi-structured, non-interventional, remote ethnographic study of patients self-administering LVSC biotherapeutics with ≥5 mL dose volumes at home. The 5 mL minimum volume was selected based on the dose volumes of currently marketed LVSC mAbs used to treat cancer (typical range: 5–15 mL), as this represents the most active area of LVSC development.[85] As SCIg was the only commercially available biotherapeutic that met these criteria at the time of study execution, all included patients were currently receiving one of several SCIg products. The LVSC oncology mAbs Rituxan Hycela® (rituximab and hyaluronidase human) (Genentech), Herceptin Hylecta® (trastuzumab and hyaluronidase-oysk) (Genentech), Darzalex Faspro® (daratumumab and hyaluronidase-fihj) (Janssen), Phesgo® (pertuzumab, trastuzumab, and hyaluronidase-zzxf) (Genentech), Tecentriq Hybreza® (atezolizumab and hyaluronidase-tqjs) (Genentech), and Opdivo Qvantig™ (nivolumab and hyaluronidase-nvhy) (Bristol-Myers Squibb), and the neonatal Fc receptor (FcRn) inhibitors Vyvgart Hytrulo® (efgartigimod alfa and hyaluronidase-qvfc) (argenx) and Rystiggo® (rozanolixizumab-noli) (UCB) were excluded prospectively, as these agents are not currently FDA-approved for self-administration, most are not administered with a delivery device, and some were not yet approved at all at the time of study enrollment. The complement protein C3 modulator Empaveli® (pegcetacoplan) (Apellis), which has been approved for self-administration of a 20 mL SC dose volume, was only recently commercialized at the time of study initiation, and patient users were unfortunately not yet available for recruitment. Other LVSC biotherapeutics available at the time of study enrollment with dose volumes smaller than the target 5 mL, such as the Repatha® (evolocumab) Pushtronex® System (Amgen), were considered out of scope.

Patients were enrolled from June 2021 to August 2021 and completed a series of activities at their own pace through a moderated, online, remote ethnography platform during the study period. Activities included closed- and open-form questions, projective exercises, and passive observation of participant-provided video and photo captures detailing current practices. All study data were collected and recorded in such a manner that the identities of the participants could not be readily ascertained. In all cases, moderators had the opportunity to follow up asynchronously to confirm observations and probe for additional details. All study procedures were conducted in accordance with the Declaration of Helsinki and its subsequent revisions.

Participant Eligibility

Eligible participants were ≥18 years of age and currently self-administering SCIg in the home setting using a drug delivery device at the time of the study. Recruiting was performed throughout the United States using commercially available, nationwide panels of patients with chronic disease. Patients were enrolled based on convenience sampling with no quotas placed on specific SCIg indications, SCIg products or manufacturers, SCIg doses, or delivery devices. Convenience sampling was employed for recruiting practicality due to the rarity of the target population and the

specialized nature of SCIg treatment. Patients were not eligible to participate if they did not have a reliable internet connection, computer, and smartphone, or if they or an immediate family member worked for a pharmaceutical company or market research firm. As one of the study goals was to inform user needs for LVSC delivery devices, patients who self-administered SCIg by "rapid push" (manual injection with a syringe alone) were also excluded.

Prior to enrollment, all participants completed a written informed consent form outlining the observational nature of the study, the requirements for participation, the intent to publish de-identified study data in a scientific journal, and the steps taken to protect their privacy throughout. Participants who expressed discomfort with taking photos and/or videos for the purposes of the study or having their de-identified study data shared for scientific purposes were excluded. All participants were compensated financially for their time, and both participants and the study sponsor were blinded to each other's identities.

Data Collection and Analysis

Participants were asked to passively video record themselves recounting prior experiences, including previous in-clinic infusion experiences and at-home infusion initiation, and performing and narrating their current practices, including ordering, storing, preparing, administering, and disposing of medications and/or supplies. To minimize disruption and best capture real-world practices, participants were free to record each of these activities at their discretion according to their own individual workflows on and around their infusion days – no specific number or length of participant-provided videos was enforced. Patient-provided video recordings were not assessed for correctness but rather to provide insight into their experiences and allow researchers to verify participant authenticity. Participants were also asked to take photos, enter open text responses, and record supplemental videos to further illustrate their overall experiences with their disease, infusions, and delivery devices.

Video and open-ended submissions were collected, transcribed, and coded by the study moderators (JH and DK). Initial coding was executed as participants completed each activity to develop an opening codebook, followed by an iterative process of reviewing and refining coding sequences to develop mutually exclusive themes by two additional researchers (CF and MC), similar to what has been described elsewhere.[86] As qualitative data accumulated for each participant, researchers continuously monitored for code saturation (the point at which no additional themes were identified) and meaning saturation (the point at which themes were fully understood and no further dimensions or nuances of issues could be discerned). Thematic saturation was determined to be reached after analysis of data from 9 participants, with an additional 2 participants included to confirm no new themes emerged. Saturation was assessed considering the study aim, sample specificity, use of established theory, quality of dialogue, and analysis strategy as suggested by Malterud et al.[87] Finally, qualitative data were compiled and grouped into themes and subthemes that described the patient experience using a similar framework to that employed by Ridgeway et al.[88] Given both the small sample size and ethnographic nature of this study, formal quantitative and subgroup analyses were not performed.

Results

Participant Characteristics

A total of 11 patients completed the remote study, all of whom were diagnosed with PIDD. The specific PIDD subtype was not captured, as it was not deemed important to the study goals. Most patients were white women between the ages of 36–65 years old with at least one year of experience using their current delivery device for SCIg infusion. Patient experience with their current delivery devices ranged from less than one year to more than five years, with the majority (72.7%) having at least three years of experience. All patients also had previous experience with intravenous immunoglobulin (IVIg) prior to transitioning to SCIg. Participants were currently infusing with one of five delivery devices: Freedom60® (KORU Medical Systems), SCIg60™ (EMED Technologies), Crono S-PID 50 (CANÈ SpA), CURLIN® 6000 (Moog Medical), or CADD-Solis VIP™ (ICU Medical), with the Freedom60 used most commonly. Most participants (63.6%) also had experience using other delivery devices prior to their current device. Patient-provided photographs of their delivery devices are available as Supplementary Material (see Data Sharing Statement). SCIg products varied between participants, with 5 infusing Hizentra® (CSL Behring), 3 infusing HyQvia® (Takeda), 2 infusing

Cuvitru® (Takeda), and 1 infusing Xembify® (Grifols). All but one of these SCIg products was supplied to participants in a vial configuration. Administration-related parameters, including dosing frequency, infusion volume, infusion duration, and number of needle sites per infusion, differed across participants, although there was an expected relationship between these factors for each patient (Supplementary Table 1). An aggregate summary of baseline participant characteristics is presented in Table 3.

Table 3 Participant Characteristics

Category	Participants (n=11)
Gender	
Female	10 (90.9%)
Male	1 (9.1%)
Ethnicity	
White	9 (81.8%)
Black or African American	1 (9.1%)
Middle Eastern or North African	1 (9.1%)
Age	
36–45	5 (45.5%)
46–55	2 (18.2%)
56–65	3 (27.3%)
65+	1 (9.1%)
Current Medication	
Hizentra	5 (45.5%)
HyQvia	3 (27.3%)
Cuvitru	2 (18.2%)
Xembify	1 (9.1%)
Current Medication Presentation	
Vial	10 (90.9%)
Prefilled syringe	1 (9.1%)
Dosing Frequency	
Every week	6 (54.5%)
Every 10 days	1 (9.1%)
Every 2 weeks	1 (9.1%)
Every 3 weeks	2 (18.2%)
Every month	1 (9.1%)
Infusion Volume	
20–50 mL	5 (45.5%)
51–100 mL	5 (45.5%)
Over 100 mL	1 (9.1%)
Infusion Duration (t)	
t < 1 hour	1 (9.1%)
1 hour ≥ t < 2 hours	5 (45.5%)
2 hours ≥ t < 3 hours	1 (9.1%)
t ≥ 3 hours	4 (36.4%)
Number of Needle Sites per Infusion	
1	1 (9.1%)
2	5 (45.5%)
3+	5 (45.5%)

(*Continued*)

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Table 3 (Continued).

Category	Participants (n=11)
Current Infusion Device	
Freedom60	5 (45.5%)
SCIg60	2 (18.2%)
Crono S-PID 50	1 (9.1%)
CURLIN 6000	2 (18.2%)
CADD-Solis VIP	1 (9.1%)
Experience with Current Infusion Device	
Less than 1 year	1 (9.1%)
1–2 years	2 (18.2%)
3–5 years	4 (36.4%)
More than 5 years	4 (36.4%)
Previous Infusion Device Experience	
Have previously used another delivery device	7 (63.6%)
Have not previously used another delivery device	4 (36.4%)

Qualitative Themes

Patients unequivocally prefer SC infusions at home to in-clinic infusions

Study participants uniformly reported that receiving infusions in clinic, whether IV or SC, placed an immense time and emotional burden on them. Patients recalled that their IV infusions could require up to 12 hours of their day to be spent at the clinic (Table 4; Q1-Q3) and they needed to account for the time spent on transportation, which could range from less than an hour to multiple hours each way for those who live in rural areas (Table 4; Q2-Q4). Patients recalled that after an initial waiting period, they would need vitals taken and an IV site placed if they were receiving an IV infusion, and pharmacies

Table 4 Preference for SC at Home

Quote ID	Participant ID	Quote
Q1	P10	"What was so time consuming was waiting for the pharmacy to bring the medicine, you know, for the IV, and sometimes I would wait two to three hours. But most of the time, I was at the hospital from 7:00 in the morning to maybe 6:00 or 7:00 that evening."
Q2	P2	"I was really under a lot of stress and the extra time driving there, even though it was only twenty or twenty-five minutes each way, it just added up and it took longer when you're in a center waiting for nurses who are busy with other patients."
Q3	P3	"I live two miles from the medical center, so it was not an inconvenience to travel to the infusion clinic to get my medication. But my infusion could take up to four hours from start to finish once the product was infused into me. Half the battle would be the time it took to get called back from the waiting room to the infusion suite to get the nurse to have completed the vitals to all of that prep time. It made the process a good afternoon process from 12:00 to sometimes I would not get out till 5:30 or 6:00."
Q4	P1	"Having to go to a clinic for my infusions would be really hard. I live in a very rural area and would have to drive almost two hours each way. It would be hard on me to make such a long drive to receive my infusions and would be hard driving so far afterwards if I did not feel well. I take Benadryl as a pre-med and it makes me very tired. I do not have anyone to be able to commit time to drive me since they all have full time jobs. It works perfectly for me to be able to do them [the infusions] in the comfort of my home in the evenings when my husband is home. It would put a strain on us trying to find someone to drive me home afterwards [after in-clinic infusions]."

(*Continued*)

Table 4 (Continued).

Quote ID	Participant ID	Quote
Q5	P3	"The decision made me feel much more empowered as a patient, and it also gave me much more control over the process, the time of the infusions, and not having to go into a clinical setting to complete the infusions once the decision was made."
Q6	P5	"If I had to do this, go somewhere and do it rather than in the comfort of my own home, I know how much more complicated my life would be."
Q7	P4	"Being able to do this at home is so nice for me and I would not be able to juggle working full time and going to a clinic right now with my schedule. And so doing it at home is convenient and guarantees my access to the treatment. I would not have access to the treatment if I had to go to an infusion center.

may wait to begin medication preparation until these steps were complete, further delaying the process. The duration of infusion was reported to be up to 4 hours for an IV infusion (Table 4; Q3). Due to the effects of pre-medications and the infusion itself, some patients required another person to drive them home, complicating the routine (Table 4; Q4).

In contrast, SC administration in the home setting was reported to reduce burden and complexity for both patients and their caregivers (Table 4; Q4-Q7). Patients described a sense of empowerment due to their ability to control their own infusion schedule and infuse in the comfort of their own homes (Table 4; Q5). Some patients even reported they would not be able keep up with their lives and work schedules if self-administration was not an option and may otherwise have to forego treatment altogether (Table 4; Q7).

Patients are often responsible for ordering their infusion supplies and medications to be dispensed; this process is burdensome and dispensing errors are common

Patients revealed that they play an active role in the ordering process for both their medications and infusion supplies. In our sample, this involved contacting the specialty pharmacy and submitting written or verbal requests for medication refills and infusion supplies, which may take a considerable amount of time and lead to frustration (Table 5; Q1-Q5). Patients reported interacting with representatives who have little to no knowledge of these specialty products, adding to the frustration (Table 5; Q1-Q2). Some patients emphasized that follow-up calls and reminders are often needed to ensure their medication and supplies are shipped on time (Table 5; Q2-Q3). Several participants also noted that changing

Table 5 Managing Medication/Supply Orders and Dispensing Errors

Quote ID	Participant ID	Quote
Q1	P4	"Ordering supplies is like one of the bigger barriers, because, again, nobody at the specialty pharmacy is familiar with HyQvia but also the person that you talk to when you're ordering supplies clearly has no medical training whatsoever."
Q2	P4	"I have to order refills myself a week before I need them, which involves calling the specialty pharmacy and speaking to a non-medical professional who never has any idea who I am or what I need to order and it's kind of like an argument every time. Probably 90% of the time I do not get the supplies that I ordered or the wrong supplies, especially needles. I try to order two of everything, so that whenever I do not get the correct stuff, I have an extra one on hand."
Q3	P1	"And one thing I have to say about the pharmacy that I am using now is it's not as easy as using a supply worksheet and they just have a list of supplies that they think I need. It took a little bit of getting used to, you know. Some of the things were a little bit different as far as pooling bags, vented spikes, and things like that. I have to follow up with this pharmacy a lot more to make sure that my medication gets sent to me on time. And I just wish that all of the pharmacies for this medication used the same pooling bags, and everything was just kind of uniform."

(*Continued*)

Table 5 (Continued).

Quote ID	Participant ID	Quote
Q4	P2	"Working with the same [pharmacy] team members to reorder medicines and things makes it easier. Because when you work with a different representative, it's like going through the whole process and it just seems like it's really overwhelming and lengthy versus just how some companies [pharmacies] do it versus others."
Q5	P2	"I get anybody [any pharmacy representative] and they kind of go through the whole thing. It's very regimented and there's no personalization. It takes much longer than it did with any of the other companies [pharmacies] before. I appreciate that they are very thorough, but it's like reinventing the wheel and it gets really frustrating that it takes such a long time to do the ordering."
Q6	P9	"One time I got a four-needle set instead of the three-needle sets. So, I called her [the pharmacist]. And because I already had the three-needle set for that week [from a previous shipment], she just changed it that following week and sent me the correct supplies because I did not need it immediately."
Q7	P3	"This package [recently dispensed supply package] came with two needles. I do not use two needles. I use four needles. Why did I get a package with only two needles? Who knows, but that's probably my friend's [package] and the specialty [pharmacy] gave me the wrong supplies."
Q8	P10	"One time they packaged the wrong syringes. They were 60 cc syringes, but they would not fit this pump [SCIg60]. There was something designed about it differently and it would not go in the pump."
Q9	P3	"The pharmacy team was not competent enough to be able to identify that when you are at 60 milliliters [dose volume], you need more than one 50-milliliter infusion syringe. So, they only provided what they had provided in the past, despite my telling them and specifically ordering double the number of syringes."
Q10	P8	"The specialty pharmacy has not been sending enough supplies and medicine every month. I have to always call them after I receive a delivery and ask them to send the rest of what I need."

providers could exacerbate the dissatisfaction, frustration, and errors associated with the ordering and shipping processes, as it disrupts the procedures they have become accustomed to (Table 5; Q3-Q5).

Beyond the requirement to place refill and supply orders, patients were also burdened with verifying that the correct infusion supplies had been dispensed. Receiving the incorrect infusion supplies was a commonly reported occurrence (36.4% of patients) even in our small sample (Table 5; Q2, Q6-9), with one patient estimating that either incorrect supplies are sent or correct supplies are omitted "probably 90% of the time" (Table 5; Q2). When this occurs, patients noted that they often use surplus supplies stored from previous infusions if they are available (Table 5; Q2, Q6). In anticipation of this issue, some patients also reported that they intentionally request extra supplies to create a stockpile at home (Table 5; Q2). Other patients stated they need to routinely make additional shipment requests due to missing products (Table 5; Q10). Patient-provided photographs and/or video stills relevant to managing medication/supply orders and dispensing errors are available as Supplementary Material (see Data Sharing Statement).

Patients are required to properly store large amounts of medication and supplies at home, prompting a variety of management strategies

As shown and described by those in our sample, medication and supply shipments can take up significant space in patients' homes. Participants reported that shipments are large, as they often contain coolers, ice packs, and other disposable packaging materials (Table 6; Q1-Q3). A single infusion for patients in our sample often required multiple syringes, needles, transfer devices, tubing sets, and additional medications other than the SCIg product (eg, pre-medications, such as acetaminophen and diphenhydramine), and some patients expressed an overall sense of overwhelm associated with the volume and complexity of required supplies (Table 6; Q4). Patients reported that they may receive the materials required for multiple infusions all at once (eg, a month supply) and must store them until their infusion days. For some patients in our sample, a month supply comprised four infusions (one infusion/week) and therefore contained significant amounts of supplies per shipment (Table 6; Q1-Q3). Several participants also reported that their pharmacies

Table 6 Storing Medications and Supplies

Quote ID	Participant ID	Quote
Q1	P5	"The shipping carton is about 16" x 16" x 20" with a styrofoam cooler. Ancillaries and medications are bagged separately. Enough meds and supplies for four doses."
Q2	P8	"My medication comes in a large cardboard box. There is styrofoam in the box and they also put an ice pack in there. Everything I need is in the box. The medicine and supplies are bagged separately in the box. I get one box in each shipment and it's a four-week supply."
Q3	P7	"Inside, everything is packaged in a styrofoam box with freezer packs and plastic bubble sheets. The medication is packaged separately from the rest of the supplies. Both medication and supplies are packed in plastic bags… usually medication and supplies for four infusions is included. Everything comes in one box/package."
Q4	P3	"The toughest part [of moving infusions to home] was probably just understanding all the supplies, how they connect together…just a little bit overwhelming in the number of supplies."
Q5	P2	"I had so many of these extra needles from my other supplier that I just use these and haven't even had them order me anymore of the needle."
Q6	P6	"The first picture [shown to the study moderator] is of my box [patient-developed organizer] where I keep one infusion's worth of medication and supplies. I fill it as soon as I have started my infusion so I am ready to go for the next time. Sometimes I am in a bit of a hurry when I am trying to squeeze my infusion into my day, so this way, I am all ready to go. The second picture [shown to the study moderator] is of my backup and surplus supplies."
Q7	P4	"I store my infusion supplies in an over-the-door shoe organizer. These are kept in my office away from anywhere where guests would be. I keep my pump hooked up to the pole ['IV pole' used to hold peristaltic pumps] simply because it is too difficult for me take down and put away between infusions. I do not like people to see any of these supplies because it looks like a hospital room!"
Q8	P1	"I keep my device and supplies in a three-drawer storage container. My medication I have to keep in the refrigerator until I'm ready to infuse and then I set it out a couple hours before."
Q9	P10	"I store my infusion device in my bathroom in a plastic drawer organizer. I do not store it alongside my medication because my medication is refrigerated…I store my medication in a small refrigerator in my kitchen."

routinely send extra supplies to account for potential use errors or product failures, or to rectify dispensing mistakes as discussed in the previous section. Some patients reported that these extra supplies are useful if they are needed but also mentioned that they can accumulate over time, especially if they are never used (Table 6; Q5-Q6).

Patients in our sample often elected to develop their own creative, self-made systems to manage their medications and supplies, such as "kits" for each infusion, or repurposing storage bins, over-door shoe racks, or carts in an effort to keep materials together (Table 6; Q6-Q9). As components have different storage requirements (ie, medications need to be refrigerated whereas supplies do not), multiple locations may be necessary. Some patients utilized specific organizers or areas of their home in order to maintain privacy and prevent guests from seeing their supplies (Table 6; Q7). In addition to infusion supplies, patients often needed to store multiple medication vials safely and correctly, placing burden on limited refrigerator space and sometimes requiring designated storage locations (Table 6; Q8-Q9). Among patients in our sample, as many as 16 vials needed to be stored at one time. As most patients only had one refrigerator in their household, medications were typically stored alongside usual refrigerated items (eg, food) and accessible to family members or guests, compromising any desired discretion. This led some patients to purchase a separate refrigerator solely for medications as an alternative (Table 6; Q9). Patient-provided photographs and/or video stills relevant to storing medications and supplies are available as Supplementary Material (see Data Sharing Statement).

Although it is required for self-administration, patient training can be variable and insufficient

Participants in our sample described initiating self-administration at home as overwhelming and reported that adequate training helped ease their anxiety associated with the process (Table 7; Q1). However, we found that training experiences

Table 7 Patient Training

Quote ID	Participant ID	Quote
Q1	P8	"Once I went from IV to SC for my infusion, the specialty pharmacy trained me. She [a nurse] taught me at home once a week over a four-week period for four infusions and showed me step-by-step what to do. I had a step-by-step quick start guidebook with more detailed information. I was nervous at first, but I did fine."
Q2	P7	"My in-home training was actually a part of my in-clinic visits, which were training visits as well as infusion visits. The training was by demonstration. They walked me through it while we were in the process of doing my first two infusions. They did it step-by-step: how the pump worked and how to activate it, how to stop it, etc. I [then] was given papers with instructions. After my training, I was really confident that I could use the device correctly because I had been trained well and given materials to refer to."
Q3	P3	"The nurse called to check on me to determine if she needed to come out again and offered to come out again. But I was pretty confident on my own and said I would call if I need any help. I have had to contact someone with a problem with my device and that interaction with the specialty pharmacy was exceptionally poor."
Q4	P9	"[The nurse] did not do any of the infusions herself but directed me on how and what to do. She watched me that first time, and after that I was on my own to do it each week. I think that home infusion companies should at least come out three to four times to make sure that the person is okay and is not having any side effects and to make sure that they do it correctly."
Q5	P2	"They actually sent me out a nurse who had never used the pump before. And I basically knew more about it than she did. She was actually Googling how to use the pump. And so that was quite discouraging."
Q6	P4	"I have an EpiPen. I actually have never used it…I've never been trained on how to use it. I've actually never even opened the box to check it out myself."
Q7	P9	"As far as training, no one trained me on any "what ifs" [troubleshooting], but I did read about them in my Hizentra therapy journal. It has an area where it's like 'troubleshooting' and that's where I read about how to fix certain things."
Q8	P4	"They really didn't teach me how to do any sort of problem solving, I had to either figure it out on my own, call the emergency line, or I would go on a Facebook webpage and ask other people that use the device how they dealt with it."
Q9	P9	"I was only confident in my skills because I looked up information on YouTube on how to do it."
Q10	P2	"On this pump [CURLIN 6000], I basically had to play with it to figure out how to stop and start because the directions are really unclear…with this whole situation, I basically have had to figure it out on my own or call into the specialty nurse line for assistance."

in our sample were highly inconsistent, with 5 of 11 participants (45.5%) reporting some degree of training inadequacy. While some patients reported positive training and support with multiple sessions and instructional material (Table 7; Q1-Q3), others reported training experiences that were suboptimal, with only a single training session in some cases (Table 7; Q4). Further, some patients expressed that the personnel responsible for training were sometimes ill-prepared to teach them how their delivery device operates, and instead, relied on online searches during the session (Table 7; Q5). Other patients reported they had no training at all on important aspects of their infusion process, such as emergency medication administration and device error troubleshooting (Table 7; Q6-Q8). If these situations occurred, patients expressed that they would often resort to publicly available resources such as Google, manufacturer websites or helplines, YouTube, or social media to teach themselves how to use their delivery devices (Table 7; Q8-Q10). Patient-provided photographs and/or video stills relevant to patient training are available as Supplementary Material (see Data Sharing Statement).

Medication preparation is complex, time-intensive, and physically demanding, increasing patient burden and error risk

The infusion preparations patients described and demonstrated in our study were complex, multi-step processes involving a variety of supplies, such as syringes, needles, vial spikes, tubing sets, and pooling bags. Tasks required for preparation included medication pooling from multiple vials into a single syringe, multiple syringes, or a bag depending on the required dose volume. Patients reported feeling overwhelmed with these tasks and nervous that they may make a mistake, which they considered a particular concern if they had any degree of cognitive impairment (Table 8; Q1-Q2). Some patients acknowledged that they frequently forget to perform recommended steps during preparation, such as wiping the tops of vials with alcohol swabs (Table 8; Q3). Despite this, all patients in our study still reported that they always prepare their infusions independently without assistance from in-home HCPs or caregivers.

Syringe manipulations, including withdrawing and expelling volumes, were sometimes reported to be burdensome to perform and particularly difficult for those with motor impairments, such as hand weakness (Table 8; Q4). Some patients attributed preparation difficulty to how their drug products are presented (eg, in vials that need to be spiked), the supplies they must use (eg, tubing sets with plastic spikes), or the specific procedure required (eg, gravity transfer to bags)

Table 8 Burdensome Preparation

Quote ID	Participant ID	Quote
Q1	P10	"At first it is very overwhelming because you don't know what you're getting into…it's just a scary thing because you never want to do anything wrong or mess up."
Q2	P9	"I think that's what took the most getting used to is doing all the steps properly. I have to do things in the same order each time and remember to unclamp each of the three needles on the set [for administration into multiple sites]. I think that's hard for me because of my issues with concentration, possibly from my autonomic dysfunction or medicines."
Q3	P2	"I have to admit, I'm pretty bad about wiping everything with the 10 million alcohol wipes that they give me… and, yes, you're supposed to wipe off the top. I frequently forget to do that. I've been pretty bad."
Q4	P8	"I've had a little difficulty filling the syringe with medication occasionally, especially if I'm tired and feeling weak, which sometimes I am."
Q5	P4	"I actually had trouble getting this needle [plastic spike on tubing set] in [the medication vial] because this is not very sharp. I feel sympathetic towards older people that have to do this themselves because it is kind of hard to get that [plastic spike] in there [the vial].
Q6	P1	"This is one thing I do not really care for…the method I have to use to get the medication from the bag. And it takes a really long time. So I have to hold it up in the air and just wait for the medication to go into the bag. It takes a while for it to empty. Just a long process here, waiting for this to empty. This just takes so long, makes my arms tired."
Q7	P9	"I do not like the fact that I have to use a mini spike to get the medicine from the vial to the syringe. I think there should be a better way than transferring from one to the other because that takes too long. And it causes a lot of air bubbles."
Q8	P5	"This [medication preparation] is probably what I consider to be the worst part of at-home infusion. This is really inconvenient and a pain to prep all this for the infusion. I am looking forward to Hizentra now coming in a prefilled syringe to make this part quicker and easier. I am looking forward to getting those and trying them out."
Q9	P2	"One of the things I have heard with other companies and other products was that they are doing prefilled syringes, which would be kind of nice."
Q10	P8	"I would love if these [medication vials] came as prefilled syringes. That would make things so much easier."
Q11	P3	"[Demonstrating the process] The prefilled syringes require the use of a fluid dispensing connector…they simply attach with a luer-lock. I am going to attach it [the prefilled syringe] to the Crono syringe and with a simple, easy tap or push of the syringe, I will load that fluid into the syringe."

(Table 8; Q5-Q6). Even with the help of dedicated supplies like vial spikes, some patients reported that pooling multiple vials into a syringe is cumbersome, time-consuming, and potentially introduces unwanted air bubbles into the drug product (Table 8; Q7). Some patients stressed that these steps are the worst part of the home infusion process as a whole (Table 8; Q8) and suggested that new product presentations, such as PFSs, may improve the experience for them (Table 8; Q8-Q10). One participant who did use a PFS confirmed that the pooling process is indeed easier (Table 8; Q11). Patient-provided photographs and/or video stills relevant to burdensome preparation are available as Supplementary Material (see Data Sharing Statement).

Priming infusion sets with medication is manual, onerous, and inconsistently performed

Priming is the process of filling the tubing (and depending on the instructions, the needle – see Table 1) with medication before administration. For patients in our sample, this involved connecting the filled medication syringe(s) to the tubing set via luer-lock and pushing the solution through the tubing by manually depressing the syringe plunger. Depending on the specific product each patient used, the priming fluid was either SCIg itself (for Hizentra, Cuvitru, and Xembify) or hyaluronidase (for HyQvia). Priming was difficult for some patients, particularly those with motor impairments, who resorted to alternative, more gross motor techniques to depress the syringe plunger (Table 9; Q1-Q2). Beyond the mechanics of syringe depression, priming practices varied considerably between patients. Some opted to push the solution to the end of the tubing (ie, up to the needle) (Table 9; Q3-Q4) while others intentionally only primed the tubing partially, with a portion of patients stating that doing so helped to reduce pain upon needle insertion (Table 9; Q1, Q5-Q8). Other patients reported that they do not prime the tubing at all, expressing that it is not needed for SC infusions and therefore unnecessarily complicates the preparation process (Table 9; Q9). Patient-provided photographs and/or video stills relevant to priming tubing/needles are available as Supplementary Material (see Data Sharing Statement).

Table 9 Priming Tubing/Needles

Quote ID	Participant ID	Quote
Q1	P10	"The way I do it [prime the tubing], since it's so hard for me to push [the syringe plunger] because I have weak hands, I just press down on the table at the end of the syringe until it gets to four inches from the needle [partially prime]."
Q2	P9	"When you are priming the line, because of the thickness [viscosity of the medication], I feel like it is very hard to push the plunger in on the syringe. I have to hold the syringe with one hand and push it with the other. Sometimes I even have to, like, put it close to my abdomen [push the syringe plunger against the abdomen] to get it going."
Q3	P9	"I push the medicine through it while watching the line. When it gets to the end of the line [up to the needle], I leave it there, clamp it off. And now the medicine is ready to be infused."
Q4	P11	"Now, you got to prime it a little bit through the tube, and I always make sure it goes to sort of by the end [up to the needle] and then I stop."
Q5	P3	If you get the Hizentra too close to the needles [when priming], it burns when it [the needle] goes in.
Q6	P5	"I push the solution up through the tubing…I stop about two inches shy of the butterfly [needle] because this solution burns like heck if you push it up to the tip of the butterfly [needle] and insert it under your skin."
Q7	P2	"I am basically going to prime the line a little bit. The key with this is you do not want to put too much in [into the tubing set] because if it [the medication] gets onto the needle, that stings and burns like heck going in. So that is not a fun thing. So I try not to do that."
Q8	P8	"Then I prime it. I get the medicine about halfway through the tubing and then I stop."
Q9	P7	"Because I am doing SC, I am not priming. I used to, but it was a pain in the neck. And it's really not necessary because this is not going into a vein. It's a minor amount of air in the tubing anyway and it [not priming] makes for a much less difficult [process]."

Needle insertion and adhesive removal are necessary but unpleasant steps for patients

Although they understood that needle insertion is required for drug delivery, patients reported significant emotional burden associated with needles, including nervousness and anxiety (Table 10; Q1-Q4). Most patients in our sample used more than one needle site per infusion, with some using as many as four, and several patients noted physical discomfort, pain, and sometimes burning upon each needle insertion (Table 9; Q5-Q7 and Table 10; Q3-Q4). Due to scar tissue development from repeated infusions, some patients needed to apply higher forces to insert their needles, leading to greater pain (Table 10; Q5). Patients in our sample employed several different strategies to minimize needle-induced pain. In addition to the partial priming technique discussed previously, some utilized lidocaine creams to reduce the pain and resulting anxiety associated with the needle insertion process (Table 10; Q4-Q5). Other strategies included ensuring proper hydration prior to the infusion (Table 10; Q6). One participant used an infusion set equipped with a soft cannula (ie, flexible plastic catheter) rather than a typical steel needle, citing reduced pain and increased comfort with this approach, particularly during movement (Table 10; Q7).

After needles were inserted, patients typically secured them in place using an adhesive dressing. Patients generally reported that the adhesive is often difficult to apply while holding the needle in their skin, with one expressing that "you feel like you need three hands" to complete this process (Table 10; Q3). Some patients felt that the removal and residual effects of the adhesive after infusion are some of the most uncomfortable and least enjoyable parts of the infusion process (Table 10; Q8). Adhesive removal was described as both painful and irritating, with multiple patients reporting itching or

Table 10 Needle Insertion/Removal

Quote ID	Participant ID	Quote
Q1	P11	"It was pretty nerve-racking. You're nervous because who wants to stick themselves with needles? But I knew that this treatment would be best for me and my family, and could sort of help me live a healthy life."
Q2	P11	"I made her [a caregiver] wait a couple minutes [with me] because I was just so nervous about sticking myself and I had to do it myself."
Q3	P2	"So I would put the needle in and then put this [Tegaderm] on. So I am going to do [grab] the needle and pinch it [skin fold on the abdomen] as such, so you get some fat [subcutaneous tissue] in there [your grip], and then you just kind of go for it [insert the needle]. It's not comfortable. You feel like you need three hands. You take your adhesive, whatever kind you are using, and you are going to place it over [the needle site]. It's not fun and I feel like a pin cushion."
Q4	P1	"I put my needle on this side. The numbing cream [lidocaine] is amazing. It really helps a lot. I wasn't using it at first and I was having some anxiety because it would burn so badly."
Q5	P4	"For the last year I have added also putting lidocaine cream on my stomach where I put the needles in because I have developed a lot of scar tissue. So it's actually really hard to push the needles into my stomach and it can hurt. So I put the lidocaine cream on so that I guess I can, like, manhandle the needles into my stomach and that makes it easier."
Q6	P10	"What's important is that you make sure you're getting hydrated because if you're not, the needles will not go in smoothly and it hurts."
Q7	P6	"I use these infusion sets [soft cannula sets] because they have a catheter [soft cannula]. The others just have a [steel] needle and when I moved, they would hurt, and I didn't like that. These [soft cannula sets] are more comfortable."
Q8	P3	"I often say one of the least enjoyable parts of anything about the infusion is removing the Tegaderm [adhesive from the skin]. I think removing the Tegaderm is actually the hardest and perhaps the most uncomfortable part of the infusion for me, and the part I least like."
Q9	P2	"I've had issues with Tegaderm. It makes me itch like crazy."
Q10	P9	"I do not use the Tegaderm that comes in the set, as I am allergic to Tegaderm."

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allergies to the most commonly used adhesive, Tegaderm® (3M) (Table 10; Q8-Q10). Patient-provided photographs and/or video stills relevant to needle insertion/removal are available as Supplementary Material (see Data Sharing Statement).

When required, delivery device programming is difficult, frustrating, and error-prone

Most patients (63.6%) in our sample used spring-based delivery devices (Freedom60 or SCIg60) that do not require programming. For the remaining participants (36.4%) who used programmable pumps (CURLIN 6000, Crono S-PID 50, or CADD-Solis VIP), all but one reported experiencing frustrations with the programming process. Some patients in our sample expressed that they were told or believed their specialty pharmacy or home infusion company would pre-program their pump for them prior to administration. However, several patients stressed that pre-programming was not performed, and they were therefore forced to manage programming themselves, which they considered challenging and not user-friendly (Table 11; Q1-Q2). One patient in particular expressed a specific desire for a pump that is ready-to-use upon startup, including the ability to automatically prime and then enter a "hold" state until the user chooses to begin the infusion (Table 11; Q2). Moreover, another patient reported that changes in dose/rate or power supply interruptions would require reprogramming of the device, which led to frustration, required technical knowledge to resolve, and resulted in failures (Table 11; Q3-Q4). Issues with programming even led this patient to refuse to recommend the device (Crono S-PID 50) to anyone who is not technically or mechanically competent, despite the device only having a limited number of buttons for programming (Table 11; Q4). Patients also reported that little support is available when programming difficulties arise, and instead, they must rely on previously supplied information or online sources that are insufficient to correctly guide them (Table 11; Q2-Q3). Patient-provided photographs and/or video stills relevant to device programming are available as Supplementary Material (see Data Sharing Statement).

Reservoir and device volume constraints pose additional preparation and administration challenges

Most of the delivery devices used by patients in our sample (ie, Freedom60, SCIg60, and Crono S-PID 50) accommodate a maximum volume of 50–60 mL per administration, as they rely on conventional or modified polypropylene syringes as administration reservoirs. Notably, no participant utilized the compatible 60 mL Medline syringe for their Freedom60 device, effectively restricting its maximum volume capacity to 50 mL for the purposes of our study. As a result, patients with doses greater than 50 mL (54.5% of our sample) were forced to prepare, load, and administer multiple syringes to complete their prescribed doses (Table 12; Q1-Q3) or use a peristaltic pump after pooling their dose volumes into a larger reservoir (ie, a bag). For affected patients, syringe volume constraints increased the time, effort, and supplies needed for

Table 11 Device Programming

Quote ID	Participant ID	Quote
Q1	P2	"If it's [CURLIN 6000] not pre-programmed, it is certainly not user-friendly and no directions are given as to how to program the pump, even though [redacted infusion company name] said that it would be pre-programmed."
Q2	P1	"I do not know if mine [CURLIN 6000] was not set up correctly, but when I go to start it, mine's on program [mode]. I will have to refer back to the paper, you know, from when they prescribed the pump for me and the settings on it. I wish that it was a little easier to get started for my infusions. I wish there was a pre-program that the pharmacy could set up that made it as easy as turning on the device and it would automatically prime itself and put on hold until I hit start to infuse."
Q3	P3	[My Crono S-PID 50 pump] needed to be programmed to address the new dose. No one from [redacted specialty pharmacy name] had acknowledged my request for help. Rather, I resorted to reprogramming the pump myself with no clinical supervision. Well, I failed at programming myself, even though I had looked online and looked on the guidance."
Q4	P3	"I would never recommend the Crono syringe to someone who is not typically comfortable with change, comfortable with technology, or gets frustrated with any type of mechanical or other objects. It does require some patience…if you take out the battery, you have to reprogram it and you have to have some level of knowledge to reprogram it. You do have to have a level of comfort given it only has three buttons. You have to know the order of the three buttons."

Table 12 Volume Constraints

Quote ID	Participant ID	Quote
Q1	P3	"When I increased my dose from 50 to 60 milliliters, the Crono is only a 50-milliliter pump and the 50-milliliter syringe [dedicated Crono syringe] is designed for that. So, now I need two syringes."
Q2	P11	"I always start with five [vials] right now. Five of the seven [vials] because my syringe only holds I believe it's 50 milliliters and each one of these [vials] is 10 milliliters. When this [syringe] is finished [infusing], I will go and then do the rest of it and start all over again."
Q3	P5	"This [administration] process here takes anywhere from forty-five minutes to an hour. So, this first syringe will be empty in the next twenty, twenty-five minutes or so. And when it is, I will remove it and then put the next syringe in and finish up from there."
Q4	P8	"It says only 50 milliliters on here [the syringe graduations], but I actually take 60 milliliters of medicine, so I open it further down [pull the plunger past the graduations]."
Q5	P10	"I am so used to having 60-milliliter syringes [when these products were previously available], so when I now infuse with 50-milliliter syringes, it doesn't change my routine. I estimate the [additional] 10 milliliters in each syringe."

both infusion preparation and administration. To avoid this, some patients intentionally overfilled syringes past their maximum labeled volumes and visually estimated the additional volume in the absence of syringe graduations (Table 12; Q4-Q5). Patient-provided photographs and/or video stills relevant to volume constraints are available as Supplementary Material (see Data Sharing Statement).

Delivery device loading is a manual, unintuitive, and technique-sensitive process

Patients described the process of loading or mounting administration reservoirs (ie, syringes or bags) into their delivery devices as highly manual and reliant on dexterity to avoid errors. For syringe-loaded devices (eg, Freedom60, SCIg60), this involved manipulating the syringe, tubing, and/or device components into their correct positions before administration. Patients reported incidents where the tubing or the syringe itself was not secured properly, leading to dislodgement, injury, or medication loss (Table 13; Q1-Q3). For some peristaltic pumps (eg, CURLIN 6000), the tubing set must be loaded precisely into the corresponding slots in the pump. Patients expressed difficulty with this process as well and imagined it would be particularly challenging for those with limited dexterity (Table 13; Q4). Patient-provided

Table 13 Device Loading

Quote ID	Participant ID	Quote
Q1	P8	"One time the syringe flew out of the device and hit me in the face. And that was because I did not wind the tab [on the Freedom60 pump] back before I put the syringe into the device. And so when I turned it on, it [the syringe] flew out and hit me in the face."
Q2	P10	"One night when I was infusing, I forgot to screw in the end of the tube that goes into the syringe real well. And so what happened was when I turned on the pump [SCIg60], my medication went all over the ceiling…there's nothing that could be done because I did not have any more medication and it's too expensive to replace it, so I had to wait till my next infusion, you know, to get the full amount of medicine."
Q3	P7	"So it's important when you put the syringe in [to the Freedom60 pump] that you set it where that [the syringe tip] hits the stop [groove on the front of the pump]. Otherwise, it's likely to shoot out when you start the pump, which is not a good thing."
Q4	P2	"I have had issues when first getting the pump [CURLIN 6000] with the little yellow part and the blue part [clips needed to seat the tubing into the pump] into these little parts [corresponding clip locations on the pump]. It's very small and fine-motor. Maybe someone with arthritis would have difficulties as far as fine-motor skills and anyone within the autoimmune kind of swelling in the hands, that sort of thing."

photographs and/or video stills relevant to device loading are available as Supplementary Material (see Data Sharing Statement).

Discussion

A summary of observed qualitative themes and their implications for delivery device design is provided in Table 14. Implications are discussed in detail in the following sections in the order in which each theme was described above.

Preference for SC at Home

Patients in our study universally preferred their current SCIg treatments at home compared to their prior experiences receiving IVIg in clinic, consistent with prior research in PIDD and other therapeutic areas.[12,70–72] Those in our sample

Table 14 Summary of Qualitative Themes and Implications for Delivery Device Design

Qualitative Theme	Implications for Delivery Device Design
Preference for SC at home: Patients unequivocally prefer SC infusions at home to in-clinic infusions	• Prioritize patient centricity throughout delivery device design, as it may offer a means to bolster existing preference for SC delivery and facilitate seamless transition of LVSC treatments from healthcare to home settings as clinically appropriate.
Managing medication/supply orders and dispensing errors: Patients are often responsible for ordering their infusion supplies and medications to be dispensed; this process is burdensome and dispensing errors are common	• Consider standardizing device components, minimizing variants, and eliminating universal connectors to reduce the risk of incorrect dispenses, inadvertent substitutions, administration errors, and use of unintended supplies. • Enforce consistent device components with predictable materials of construction by design to reduce the risk of drug incompatibility. Assess the need for change control on fluid path components, similar to controls placed on prefilled primary containers and AI/PFS devices. • Pursue prefilled or pre-prepared drug products as a primary risk mitigation strategy, especially if accompanied by strong controls over other ancillary supplies.
Storing medications and supplies: Patients are required to properly store large amounts of medication and supplies at home, prompting a variety of management strategies	• Minimize required manipulations (eg, using prefilled configurations) or eliminate patient preparation altogether (eg, pharmacy pre-preparation) wherever possible to reduce both supply storage burden and the risk of accumulating "stored waste" in patients' homes. • Consolidate supply subcomponents into single assemblies that can be packaged, sterilized, and provided to patients as single units, reducing the total inventory of components both in dispensing pharmacies and patients' homes.
Patient training: Although it is required for self-administration, patient training can be variable and insufficient	• Strive for high device intuitiveness by design, especially with regard to troubleshooting, as consistent and universally adequate patient training may not always be available. • Anticipate that current in-person training approaches may be impractical or infeasible if LVSC therapies expand into new and more prevalent therapeutic areas.
Burdensome preparation: Medication preparation is complex, time-intensive, and physically demanding, increasing patient burden and error risk	• Pursue prefilled or pre-prepared drug products whenever possible to reduce patient preparation burden. • Prioritize designs that minimize the number of patient manipulations if they are required, particularly those that depend on ample dexterity, fine-motor strength, or cognitive ability.

(*Continued*)

Table 14 (Continued).

Qualitative Theme	Implications for Delivery Device Design
Priming tubing/needles: Priming infusion sets with medication is manual, onerous, and inconsistently performed	• Acknowledge that there is no clear consensus on recommended priming practices or requirements for LVSC delivery. Without harmonization, discrepancies will exist for different products and between individual patients, even those using the same delivery devices, increasing the potential for patient-developed techniques and workarounds. • Strive to make any priming steps unobtrusive, subsumed by more intuitive use steps, or even completely passive for patients, avoiding steps that are manual, technique-sensitive, or potentially painful if performed incorrectly.
Needle insertion/removal: Needle insertion and adhesive removal are necessary but unpleasant steps for patients	• Favor designs that best minimize inevitable discomfort associated with needle insertion and avoid reliance on strong or irritant adhesives for site securement whenever possible. • Eliminate the need for "add on" adhesive or securement components to achieve adequate site retention; instead, combine components and use steps whenever possible to simplify the process, reduce removal burden, and accommodate those with dexterity limitations. • Evaluate the potential use of soft cannula infusion sets for LVSC applications systematically, as these alternatives may allow for simplified insertion, greater mobility during infusion, and reduced overall discomfort compared to typical steel needle infusion sets.
Device programming: When required, delivery device programming is difficult, frustrating, and error-prone	• Preserve flexible administration functionality without requiring manual programming inputs from patients. Currently, delivery flexibility may be difficult to accurately and reliably replicate with non-programmable pumps, although this benefit is offset by the complexity, risks, and patient burdens associated with programming steps.
Volume constraints: Reservoir and device volume constraints pose additional preparation and administration challenges	• Target designs that can accommodate a wide range of fill volumes with a single device, allowing for dosing flexibility while minimizing the impact of crossing reservoir volume breakpoints.
Device loading: Delivery device loading is a manual, unintuitive, and technique-sensitive process	• Ensure any device loading steps are intuitive, error-proofed, and able to be performed reliably without requiring significant fine-motor dexterity. Preventing the possibility of using incompatible supplies by design may help to achieve this goal.

Abbreviations: SC, subcutaneous; LVSC, large-volume subcutaneous; AI, autoinjector; PFS, prefilled syringe.

attributed that preference to both practical benefits (eg, avoidance of travel) and emotional benefits (eg, control over treatment, setting, and timing), rationales that have also been reflected by a large, systematic review of patient preference for IV vs SC treatments.[12] Similar preference for SC treatments has been observed in oncology therapeutic areas, both when IV and SC treatment options are administered in clinic[9,89] and when home administration has been explored.[33,36,37] Notably, however, most studies of at-home treatment with SC oncology biotherapeutics required administration from a trained HCP, and those that evaluated the feasibility of self-administration supplied patients with pre-prepared syringes and/or dedicated HCP education.[90,91] As all SC oncology biotherapeutics are currently supplied in vials for administration with conventional syringes, it remains unclear how preference for self-administration would compare in the absence of patient-centered delivery devices.

Our study may serve as some indication that a portion of patients will struggle with purely manual administration (eg, by hand from a syringe), as several in our sample expressed difficulties even with the comparatively less manually demanding delivery devices they currently used for self-administration. While patients who self-administered SCIg by

rapid push were excluded from our study by design, several authors have suggested that patients may have difficulty pushing syringe plungers with viscous Ig products.[74,75,92] Similar difficulties with vial and syringe presentations have also been observed among HCPs, resulting in increased risk of preparation errors[93] and musculoskeletal injuries.[94] In both settings, PFS devices may offer preparation convenience and efficiency, but would likely suffer from the same manual administration disadvantages as disposable syringes filled from one or more vials. As more LVSC treatments are explored and become available for self-administration at home, the availability of patient-centric delivery devices may offer a means to bolster existing preference for SC delivery and facilitate seamless transition from healthcare to home settings as clinically appropriate.

Managing Medication/Supply Orders and Dispensing Errors

Operational issues with medication and supply ordering were consistently reported by several patients in our sample, sometimes leading to treatment complications. This was somewhat surprising, given how well established SCIg is in the treatment of PIDD and how few patients are treated with SCIg relative to more commonly used therapies that pharmacies routinely manage. One possible explanation is that operational issues are exacerbated by the patient-specific dosing and delivery device supply requirements of SCIg, which are typically not considerations for more conventional, small-volume SC products supplied in PFS or AI configurations.

Some concerns raised in our sample are fairly unique to the types of devices patients used, such as the propensity for device supplies to be sporadically replaced with different products over the course of therapy.[95] In healthcare settings, changes to inexpensive commodity supplies are expected, whether due to shortages, stockouts, cost reduction efforts, or other factors. In such cases, universal components, such as luer-lock connectors, are highly desirable, as they allow HCPs to readily interchange supplies while preserving functional intent. However, as demonstrated in our study, while this practice allows for flexibility for suppliers and specialty pharmacies, it also increases the risk of dispensing errors, creates uncertainty for patients, and could result in delayed, incorrect, or missed doses. In contrast to HCPs who are accustomed to supply changes, patients may be confused and frustrated by them, even if they have no functional impact on drug delivery, as they have comparatively less experience and confidence to manage these discrepancies. Worse, changes to particular supplies (eg, luer-lock flow restrictors used with certain delivery devices)[96–98] may be unrecognizable to patients but could indeed substantially impact drug delivery parameters. This risk should be contemplated in the context of future LVSC therapies, as some may require variable doses akin to SCIg and demand similar if not more careful coordination between the patient and pharmacy to ensure dispensing is performed correctly. Dose timing may be especially critical for biotherapeutics used to treat cancer, as treatments are typically delivered in regimented cycles that are often contingent on patient monitoring parameters or the administration of other medications.[99–102]

Further still, many venous access devices (VADs) also rely on universal luer-lock interfaces and, while likely rare among patients receiving SCIg, are commonly used to administer anti-cancer agents,[103] including those that are frequently given alongside SC oncology biotherapeutics.[99–102] As a result, wrong-route errors (eg, inadvertent administration of SC agents intravenously) facilitated by luer-lock interfaces could present new and potentially serious risks[104] if existing supplies are used for at-home, self-administration of SC oncology agents. This may be particularly true for products available in both (but distinct) IV and SC formulations[105] or in scenarios where patients are receiving both IV and SC medications as part of their treatment regimens.[99–102] Future drug delivery devices should therefore consider standardizing device components, minimizing variants, and eliminating universal connectors to reduce the risk of incorrect dispenses, inadvertent substitutions, administration errors, and use of unintended supplies.

Finally, beyond its potential impact on drug delivery parameters, use of variable and uncontrolled supplies may also pose unforeseen drug compatibility issues. As an example, closed-system transfer devices (CSTDs), adaptors designed to prevent leakage or aerosolization of potentially hazardous drug products, can compromise physiochemical stability and dose accuracy when used to prepare or administer biotherapeutics.[106–109] In some cases, these concerns have led industry working groups to actively recommend against the use of these adaptors to ensure the integrity and correct dosing of their drug products.[110] While no patient in our study used a CSTD during preparation (SCIg is not a hazardous drug), comparable concerns may exist with similar supplies, especially given variability in their materials of construction, selection by pharmacies, and use by patients. This further underpins the need to enforce consistent device components

with predictable materials of construction by design and potentially establish change control on fluid path components (ie, similar to prefilled primary containers and AI/PFS devices) to reduce the risk of drug incompatibility. Pursuing prefilled or pre-prepared drug products could serve as a primary risk mitigation strategy, especially if accompanied by strong controls over other ancillary supplies.

Storing Medications and Supplies

The need for ancillary supplies (eg, syringes, needles, spikes, tubing sets, bags) that are decoupled from the drug product and in some cases, the delivery device, created a host of challenges in our study. Beyond the risks associated with incorrect or incompatible supplies discussed in the previous section, receiving and storing supplies placed a significant, ongoing burden on patients in our sample. A prior evaluation of patient experience with SCIg reported similar findings, concluding that managing and storing supplies was a major contributor to burden of treatment.[79]

Patients in our study reported considerable bulk to manage, owing to their pharmacies' propensity to repackage separately supplied components together for convenience, provide enough medication and supplies for every dosing interval, and accommodate different storage conditions in the same shipment. Moreover, to prospectively address inevitable errors or supply failures, pharmacies often sent (and patients often requested) frequent "backup" supplies. While this is seemingly practical, it resulted in substantial supply accumulation in patients' homes. This degree of "stored waste" observed in our study was well in excess of quantities needed for each dosing interval or episodic component replacement. Such waste may have implications that extend beyond individual patient burden and may affect the long-term environmental sustainability of this use model, especially as the topic gains increasing attention in the industry.[111] Unlike most disposables, these supplies are manufactured, sterilized, purchased, shipped, and stored, but are not always used by patients. Thus, it may be possible that the per-infusion sustainability impact not only includes the actual supplies consumed, but also a portion of the *extra* supplies dispensed that are never or seldom consumed. Quantifying the impact of stored waste was not conceived in this study but deserves dedicated focus in future research.

Regardless, minimizing required manipulations (eg, using prefilled configurations) or eliminating patient preparation altogether (eg, pharmacy pre-preparation) wherever possible would presumably help to reduce both supply storage burden and the risk of accumulating stored waste in patients' homes. Consolidating supply subcomponents into single assemblies that can be packaged, sterilized, and provided to patients as single units may also help to reduce the total inventory of components both in dispensing pharmacies and patients' homes.

Patient Training

Patient experience with onboarding, education, and training was highly variable in our sample, with some participants describing very positive interactions and others noting significant shortcomings. Negative experiences included insufficient training sessions, lack of trainer preparedness or competence, and absence of instruction on navigating rare occurrences or troubleshooting altogether, forcing patients to seek out their own sources to resolve issues. Patient education and training are considered requirements per clinical guidelines for SCIg therapy,[48] provisioned for in the Medicare durable medical equipment (DME) and home infusion therapy services benefits,[112,113] and specified in clinical programs in both the US and Europe.[92,114,115] Ensuring accessible and high-quality training has also been associated with higher treatment satisfaction.[78]

While most quantitative surveys of patients self-administering SCIg suggest that patient training is adequately conducted, variability has still been observed in areas consistent with our findings, with some portion of patients reporting training difficulty, dissatisfaction, barriers, nonconfidence and/or lack of trainer competence.[66,78,116] The need for better troubleshooting and error state resolution has also been reinforced by a qualitative study of treatment burden in patients receiving facilitated SCIg, where some patients expressed that they were left to figure out how to resolve pump alarms on their own.[79] Moreover, similar variability in training practices has been observed in other therapeutics areas with simpler, small-volume SC delivery devices, including lack of education on nuanced error states and patient propensity to seek out their own resources, even if they are not accurate.[117,118] These studies also draw attention to the variable and oftentimes limited training HCPs themselves receive on how drug delivery devices should be properly used. Nursing guidelines for SCIg administration express comparable sentiments, specifically noting that

standard curricula for nursing education programs do not provide the level of detailed infusion therapy training necessary for administering and managing Ig therapies.[119] Taken together, these sources suggest that existing gaps may be attributable to limited healthcare resources (eg, HCP time, HCP training on devices, dedicated staff), which may become further constrained or even unscalable if LVSC therapies expand into new and more prevalent therapeutic areas. To address this prospectively, future devices should strive for high device intuitiveness by design, especially with regard to troubleshooting, as consistent and universally adequate patient training may not always be available.

Burdensome Preparation

Patients in our sample expressed that preparing their medications for infusion at home presented a variety of challenges. Some issues were due to product presentation and required supplies (eg, pooling multiple vials using vial spikes, transferring contents into bags) and others were simply related to the process of performing manipulations at all (eg, remembering steps, filling syringes). Difficulties were particularly evident among those with cognitive or motor impairments. Syringe manipulation was specifically mentioned as a pain point in our study and has been similarly noted in prior literature on patient challenges with manual SCIg injections.[74,75,92] Consistent with our findings overall, preparation complexity, anxiety associated with performing steps correctly, and need for adequate coordination, dexterity, and hand strength, have also been described elsewhere as contributors to burden of treatment for patients self-administering SCIg.[79,95,120] In contrast, shorter preparation durations have been associated with higher treatment satisfaction scores,[78] although the average preparation time among SCIg users is still estimated to be approximately 36 minutes.[121]

Some, but not all, of the preparation burden described in our study could be alleviated by the use of prefilled product configurations (eg, PFSs), and several patients in our sample specifically noted a desire to have their products supplied prefilled. The potential benefits of PFS configurations are already well-described[122] and a recent survey of SCIg vial vs PFS users confirmed that PFSs were associated with significantly shorter infusion preparation times compared to vials.[66] Notably, however, PFS users in this survey had lower global treatment satisfaction scores compared to vial users, which the authors attributed to the lack of availability of larger-volume, pump-compatible PFSs (20 mL and 50 mL) at the time of study and the associated patient requirement to perform multiple tip-to-tip transfers to conventional polypropylene syringes. Whether this concern is completely attenuated by the current availability of larger-volume PFS configurations remains unknown, although it is expected that many patients will still require multiple-syringe administrations, given that a reported 53% of adult SCIg patients receive more than 10 grams (ie, more than 50 mL of 20% solution) of Ig per infusion.[121]

Still, one element that remains a challenge for prefilled products is the ability to accommodate variable-dosed (ie, not fixed-dose) medications. For SCIg, this is accounted for by making several vial or syringe presentations available, as doses are typically rounded to the nearest vial or syringe size and ultimately managed by patients at the point of use.[123,124] However, for prefilled biologic-device combination products that are designed to deliver fixed doses, this situation often necessitates separate device variants for each dose, as evidenced by several products currently supplied in AIs/PFSs.[17] More complex still would be medications that require truly precise, weight-based or otherwise patient-specific doses that cannot be rounded as SCIg is. For example, while many oncology biotherapeutics can be administered in fixed doses[23,125] this approach may not be appropriate for all molecules[126] and dose-escalation studies (ie, evaluation of several, gradually increasing doses) are still commonplace during clinical development to determine exposure–response relationships.[25] Such cases where dose variability is required may warrant exploration of other use models, such as pharmacy filling (ie, rather than manufacturer filling) for home use, which has been established for select products that require highly patient-specific dosing.[127]

Lastly, while not specifically evaluated here, patient-developed routines and rituals have been identified as coping strategies to ease the burden of self-administration in both SCIg users[74,81] and elsewhere in small-volume self-injection.[128] Purposeful future exploration of these practices among patients receiving LVSC therapies could potentially reveal new strategies to improve patient experience. Overall, our study and others suggest that future devices should pursue prefilled or pre-prepared drug products whenever possible to reduce patient preparation burden. If infeasible, manufacturers should prioritize designs that minimize the number of required patient manipulations, particularly those that depend on ample dexterity, fine-motor strength, or cognitive ability.

Priming Tubing/Needles

The tubing/needle priming process was also a significant pain point described in our study, with several patients citing technique-sensitivity and issues such as difficulty pushing syringe plungers and pain associated with priming medication to the end of the needle. In some cases, these concerns caused patients to deliberately prime the tubing only partially or abandon priming altogether to simplify the preparation and administration processes. These priming struggles are consistent with large-scale evaluations of patient-reported outcomes in those receiving SCIg, where a portion of patients noted priming as their greatest training concern.[66,116] Nursing guidelines also emphasize that priming can be highly technique-sensitive and a key consideration for certain SCIg administration approaches.[95] As mentioned previously, challenges associated with depressing syringe plungers, particularly with viscous medications, are commonly cited in the literature,[74,75,119] and some authors even suggest that difficulty with manually pushing syringes could preclude patients from using certain needle types or delivery methods.[92]

Regarding priming volumes, a "dry priming" technique (intentionally stopping fluid approximately 1 to 1½ inches before the needle) is explicitly recommended in some SCIg nursing guidelines to avoid pain and site reactions.[67,92,119] This practice is consistent with many of the patient demonstrations and accounts in our study and also reflected in some (but notably not all) SCIg product Instructions for Use (Table 1). However, patient-reported techniques such as leaving a greater volume of residual air in the tubing or entirely omitting priming deviate from both guideline and product-specific priming recommendations. These deviations are potential areas for future exploration, as it is unclear from our small sample if such priming variations are more widely practiced and whether they have any implications on medication efficacy or tolerability. Interestingly, one SCIg nursing guideline recommends that after the infusion, some patients can inject a small amount (5 cc) of air into the tubing to flush the line and create an air lock at the end of the needle,[92] suggesting that small volumes of air injected SC are unlikely to pose major concerns. A similar "air sandwich" technique (pulling air into the needle, followed by drug, followed by air into the bottom of the syringe barrel) has also been recommended for the administration of SC oncology agents to prevent leakage after injection.[27]

Altogether, lack of consensus and inconsistencies in practice indicate that priming remains a clear area of improvement for current devices and warrants consideration for future devices that may require it. Notably, in the context of pump programming (described in a subsequent section), one study participant expressed a desire for a device that would "automatically prime itself" to make this step completely free from user interaction. This type of use model appears ideal, and if possible, device manufacturers should strive to make any priming steps unobtrusive, subsumed by more intuitive use steps, or even completely passive for patients, avoiding steps that are manual, technique-sensitive, or potentially painful if performed incorrectly.

Needle Insertion/Removal

Unsurprisingly, activities surrounding the use of needles were among the most frequently cited pain points in our sample. Needle phobia and associated anxieties with self-injection have been exhaustively characterized[50] and similarly noted as significant concerns among patients self-administering SCIg.[66,116] Needle-related patient concerns in our sample can be broadly categorized into two groups: those associated with needle insertion itself (eg, pain, burning, overall discomfort) and those associated with the adhesives used to ensure site integrity and proper medication delivery.

In terms of needle insertion, patients clearly expressed that this process is uncomfortable, nerve-racking, and cumbersome, and although they would like to avoid it, accepted that it is a requirement for their treatments. Desire to minimize needle insertions as much as possible is strongly supported by several large discrete choice studies, where the notion of fewer needle sticks was a major driver of treatment preference for patients receiving Ig,[70–72] particularly among those with longer disease histories.[72] Several patients in our sample mentioned that using numbing creams containing local anesthetics, a technique that has also been described in nursing guidelines for SCIg administration,[92,119] can make the needle insertion process significantly more tolerable. Others noted that using an infusion set with a soft cannula rather than a typical steel needle created a more comfortable experience. Soft cannula products are widely used for insulin delivery[129] and have also been successfully employed to deliver LVSC infusions in clinical trials,[130] but are not commonly discussed in the context of SCIg.[58]

In addition to the increased perception of comfort observed in our study, soft cannula infusion sets may also address some of the ergonomic challenges (eg, the need for "three hands") raised by patients in our sample, as these products typically have integral adhesives and assisted or guided insertion mechanisms.[131] Further, novel soft cannula designs that can be left indwelling for extended durations and mitigate adverse events during wear are becoming increasingly available.[132] Still, as most SCIg delivery devices currently have corresponding steel needle infusion sets, it is unclear how widely used soft cannula sets are in this patient population or how broadly compatible they are with existing devices. Future studies may therefore be warranted to more systematically evaluate the use of soft cannula sets for LVSC applications.

Interestingly, while patients in our sample certainly expressed discomfort during needle insertion as discussed, a roughly equal number complained about site securement, with some even insisting that using or removing adhesives is the most uncomfortable part of the infusion process. Issues with adhesive securement and skin irritation/sensitivity have also been reported elsewhere, including cases of needle displacement due to adhesive failure[58] and recommendations to avoid product use in patients with potential adhesive allergies.[133] Other literature has suggested that adhesives may pose additional complications for specific delivery devices during LVSC infusion, such as false pump occlusion alarms if the adhesive is pulled too taut[95] or wearable device dislodgement if the adhesive fails to withstand administration-related tissue swelling.[130] Notably, the latter scenario may require use of stronger adhesives, which patients in our sample were adamantly opposed to. Moreover, use of creams, lotions, or ointments, which was prevalent in our sample, may exacerbate such adhesive securement issues. Indeed, the Instructions for Use for one currently approved non-biotherapeutic OBI product specifically warns users not to apply lotions, oils, or ointments at the injection site,[134] presumably to avoid interactions with the device adhesive. Ultimately, our study suggests that device manufacturers should favor designs that best minimize inevitable discomfort associated with needle insertion and avoid reliance on strong or irritant adhesives for site securement whenever possible.

Device Programming

Device programming practices were variable among patients who used programmable delivery devices in our sample. In most cases, patients expressed that their pumps were intended to be programmed by their pharmacies or home infusion providers but there were several instances where this was either missed or circumstances arose that required them to take on programming responsibility themselves (eg, a change in dose or interruption of power). Affected patients reported that in such events, their designated support channels (eg, pharmacy, home infusion provider, supplied educational materials, or online sources) were either unavailable or unable to provide adequate assistance, and they struggled and sometimes failed outright as a result. These patients insisted that performing programming is not a reasonable expectation and should be easier, condemning programming steps as not user-friendly and requiring technical competence to complete. Fewer programming steps also did not seem to change this sentiment, as some patients still felt burdened by devices with limited programming options (eg, Crono S-PID 50) compared to others (eg, CURLIN 6000, CADD-Solis VIP). Instead, patients explicitly stated that an ideal system would perform any programming and setup steps completely passively, including priming, as discussed above.

Surprisingly, practices and issues related to device programming among patients self-administering SCIg are sparsely discussed in the literature. One large-scale survey conducted by the Immune Deficiency Foundation reported that patients' physicians are typically the ones responsible for determining the rate of SCIg infusion, but responsibility for pump programming itself was not mentioned.[121] Another study noted that *reprogramming* conventional peristaltic pumps is mandatory for facilitated SCIg administration to avoid pump occlusion alarms, although it similarly did not specify who is responsible for this step.[135] Along with easy programmability, the study authors recommended that other attributes of an ideal home infusion pump should include minimized size and noise, long battery life, and flexibility for dose/rate titrations.

Outside of SCIg, large observational studies and systematic reviews have demonstrated that pump programming errors still occur even among trained HCPs using smart infusion pumps (ie, those equipped with pre-programmed drug libraries),[6,136–138] and would presumably be at least as common among patients using devices without such safety features. While it did not quantify programming error rates, one exploration of user-friendliness of home care technologies, including IV infusion pumps, did find that older patients in particular were not comfortable with the electronic components of the studied

programmable pump and struggled with the physical and cognitive demands of using it.[139] Impaired ability to read digital screens was specifically noted, and none of the home technologies in this study were ultimately considered truly user-friendly by patients. Lack of intuitiveness of programming displays and display malfunctions have also been considered by regulators, who recommend specific evaluation of how these failures could compromise safe operation of infusion pumps.[140,141]

Of course, alternatives to programmable pumps, such as the Freedom60 and SCIg60 devices, also exist and were frequently used by patients in our study. These systems employ different forms of rate-controlled tubing sets that provide fluidic resistance against constant-pressure drive mechanisms (ie, springs), therefore regulating flow. This is accomplished with either an adjustable dial on the tubing set or through selection of one of several (up to 20) tubing set flow restrictor variants, each of which is intended to achieve a target flowrate. In either case, the actual flowrate is a function of the selected fluidic restriction (ie, target flowrate) and other fluidic influences, such as temperature, barometric pressure, solution viscosity, and infusion equipment or conditions (eg, pump, syringe, tubing components, number of needles, vertical distance between pump and injection site, physical activity, etc).[96,98] As a result, flowrate variability is *expected*, as it is specifically noted in approved product Instructions for Use[61,96] and has been reported in practice.[142,143] The limitations of constant-pressure drive mechanisms, including flowrate variability and overall lack of flowrate regulation, compared to more sophisticated systems has also been described in the context of other delivery devices, such as wearable infusors.[77] While flowrate variability may have little pharmacokinetic impact for some but not necessarily all biotherapeutics,[25,130,144,145] unexpected variation in infusion duration may still be disconcerting for patients[142,143] and potentially affect how they schedule or behave during administrations. The exact impact that these and other factors have on actual or desired activities during infusion was outside the scope of this study, however, and warrants future exploration.

Finally, the need for multiple flow restrictor component variants may also contribute to the supply burden, environmental sustainability impact, and risks of incorrect supply usage discussed in the sections above. All things considered, our observations suggest that programmable pumps preserve valuable delivery flexibility that may be difficult to accurately and reliably replicate with non-programmable pumps. However, this benefit is offset by the complexity, risks, and patient burdens associated with programming steps. Future devices should therefore strive to achieve flexible administration functionality without requiring manual inputs from patients.

Volume Constraints

As described above and referenced in Table 2, available devices for SCIg administration are often broadly categorized into two groups – syringe driver pumps and peristaltic pumps – with pump choice dependent on a variety of factors, including Ig product, administration volume, insurance coverage, and patient preference.[92,95,135] Technical distinctions (eg, drive mechanism, control method, programmability) between these pump types aside, the total volume capacity of the pump reservoir has an important impact on required preparation and administration steps. For example, most commonly used syringe drivers have maximum volume capacities of 50–60 mL,[59,92] as a compatible syringe must be loaded into the pump in a specific orientation. To the extent they are available, larger syringes or other rigid containers simply cannot fit into these systems for proper administration and require other purpose-built syringe pumps with bespoke containers filled at point of use (eg, Crono S-PID 100). In contrast, many peristaltic pumps can accommodate reservoirs that are on the order of hundreds of mLs, limited only by which flexible container is selected from numerous available options (eg, 25 mL, 50 mL, 100 mL, 250 mL, 500 mL, 1000 mL, etc).

More than half of patients in our sample infused SCIg dose volumes greater than 50 mL, and therefore required multiple (ie, sequential) syringe reservoirs per administration if they did not use a peristaltic pump. To avoid additional preparation and administration steps, several of these patients resorted to overfilling their syringe reservoirs beyond their maximum measurable volumes, risking inaccurate dosing and potential leakage due to plunger dislodgement. While the goal of this study was not to quantify such risks, many patients are likely to face this use case, as more than half of patients receiving SCIg reportedly require dose volumes that will exceed a 50 mL syringe capacity even with highly concentrated products.[121] Some patients in our sample opted for or were recommended to use peristaltic pumps as alternatives to sequential syringe administrations, pooling their larger dose volumes into single flexible bag reservoirs instead. However, potential tradeoffs between the consequences of volume constraints and risks associated with more complex devices cannot be adequately weighed using

our small sample alone, and future, large-scale studies are needed to properly evaluate these factors as they relate to device preference.

Further, the variable-dose nature of SCIg may exacerbate inherent issues posed by reservoir volume constraints. Unlike most biologic-device combination products that are consistently dosed as fixed volumes for the duration of therapy, even a marginal increase in SCIg dose could cause a patient to cross the volume "threshold" imposed by syringe reservoir capacity. This occurred several times in our sample, where any dose volume change beyond 50 mL required the addition of another syringe per infusion. Notably, adding an additional syringe is the correct method to ensure accurate dosing, though some patients opted for the "overfilling method" described above specifically to avoid having to use additional syringes.

Limited reservoir capacities and/or variable dose volumes have presented issues for other delivery devices as well. In a study comparing an investigational wearable infusor vs the Crono S-PID 50 infusion pump for SCIg administration, the combination of variable doses and device volume capacities limited to 10 or 20 mL required the use of 2–5 (median 3) wearable infusors per weekly infusion.[77] Despite patients preferring the wearable infusor to the Crono S-PID 50 pump in this study, the authors concluded that the need for multiple, single-use devices per dosing interval could pose substantial economic or sustainability challenges. In this case, device disposal necessarily implied discarding both the medication reservoir and power system (ie, mechanical components) for each wearable infusor, which was multiplied by the number of devices required at each volume breakpoint. The same would be true for other single-use, self-contained devices, such as those with motors, batteries, or other electronic components. These concerns may still be prohibitive even with fewer/smaller wearable devices, as one manufacturer recently discontinued plans to commercialize an electromechanical OBI product that required only two devices per dosing interval.[47] In light of all of these factors, device manufacturers should ideally target designs that can accommodate a wide range of fill volumes with a single device, allowing for dosing flexibility while minimizing the impact of crossing reservoir volume breakpoints.

Device Loading

Finally, similar to other steps in the preparation and administration process, patients in our sample reported that loading reservoirs or other components into their devices was technique-sensitive and could result in failures if not performed correctly. This was true for both syringe driver and peristaltic pumps, although the Freedom60 pump was the most frequently implicated device. In particular, several patients cited instances where the syringe or the medication itself would be inadvertently ejected from the pump if the components were not properly fastened. This issue has also been reported in product complaints for this device.[146,147] While some of these failure modes may be attributed to unclear user feedback or the force/dexterity required to perform syringe loading correctly as observed in our study, others may be related to the use of incompatible supplies with the Freedom60 device, which has already been discussed in detail in prior sections. Specifically, the flow restrictors (Precision™ Flow Rate Tubing) used to regulate infusion rate each contain an integral luer disc that mates with a groove on the pump nose to retain the restrictor (and thus the syringe) in place.[96] If a different product is used or the tubing set is connected directly to the syringe without this component, its functions to control the flowrate, prevent unintended rapid delivery, and secure the syringe to the pump nose are compromised.

For peristaltic pumps, patient complaints in our study mostly centered on the fine-motor steps required to load tubing elements into the pumps. Although patients specifically attributed this issue to the CURLIN 6000 pump, similar issues with seating tubing or medication reservoirs have been observed for other peristaltic pumps, including CADD pumps. For example, difficulties or errors associated with latching CADD cassettes to their respective pumps, resulting in alarms signaling improper cassette attachment, have been reported in product complaints.[148,149] Overall, patient complaints in our study and elsewhere suggest that any device loading steps should ideally be intuitive, error-proofed, and able to be performed reliably without requiring significant fine-motor dexterity. Preventing the possibility of using incompatible supplies by design may also help to achieve this goal.

Limitations

Our study has several limitations. First, the small sample size and qualitative, observational design of this study warrant larger, prospective studies to confirm our observations and explore how they may vary across different patient subgroups.

Similarly, our sample was primarily composed of white women, reflective of convenience sampling of patients available on nationwide recruiting panels rather than the population epidemiology of SCIg users, which may limit the overall generalizability of our findings to broader patient demographics. While necessary to access sufficient study participants, convenience sampling may have also been a source of self-selection bias independent of demographics, with potentially more engaged or motivated patients being overrepresented. Our sample also largely consisted of those who have been self-administering SCIg for many years. While this allowed patients to draw from a wealth of experience, including how their process has evolved over time, it also required them to report on events that may have occurred long ago (eg, initial training), increasing the risk of recall bias.

SCIg was chosen as the primary focus of our study to inform other potential LVSC use cases and delivery devices, as it is the most established LVSC biotherapeutic available on the market. However, while SCIg represents many of the potential axes of variability in LVSC therapy characteristics in line with our study intent, there are some elements of the SCIg use process that may not always be generalizable to all LVSC therapies. Examples may include patient-specific dosing, instances of very large dose volumes (eg, hundreds of mLs), patient preparation requirements (eg, manipulating drug vials), and use of general-purpose PIP devices rather than purpose-built delivery devices. To encompass other potential LVSC use cases, such as those with relatively smaller volumes (eg, 2.25–5 mL) and/or different device types, our sample would have ideally also included patients using other products, such as the Empaveli (pegcetacoplan), Repatha (evolocumab), Skyrizi® (risankizumab-rzaa) (AbbVie), and Furoscix® (furosemide) (scPharmaceuticals) OBIs. Unfortunately, however, most of these products were either not yet approved or no patient users could be identified for recruiting at the time of study enrollment. Future studies should also consider these use cases to understand their similarities and differences, and broaden applicability to more LVSC treatments as they continue to become available.

Conclusion

Although LVSC administration at home is largely preferred to the alternatives, the current SCIg use process presents a variety of challenges for patients. In our study, the most salient pain points were those related to: managing medication/supply orders and dispensing errors; storing medications/supplies and associated waste; troubleshooting device issues due to insufficient training; performing burdensome medication preparation steps; priming tubing sets manually; inserting and securing steel needles; programming delivery devices; adapting to device volume constraints; and properly loading reservoirs or tubing into delivery devices. These challenges represent concrete barriers to optimal LVSC self-administration that emerged consistently across our sample, and reveal how seemingly small design decisions have the potential to substantially impact patient experiences with LVSC therapies. While not all of these factors will apply to every LVSC scenario, these insights, along with their corresponding implications for device design, provide a framework to inform user needs for LVSC self-administration, anticipate obstacles during development of new LVSC therapies, and improve existing delivery devices. As LVSC delivery continues to expand to more prevalent disease states and complex therapies, addressing the unmet needs observed in this study may become critical for successful at-home adoption and effective use.

Data Sharing Statement

The Supplementary Material for this study consists of one Supplementary Table (available with this publication) and a comprehensive collection of anonymized, participant-provided photographs and video stills referenced throughout the manuscript. Due to file size limitations, these high-resolution images have been deposited in an external scientific repository and can be accessed upon request. These images provide visual documentation of real-world practices with self-administered SCIg that support and contextualize the findings presented in this manuscript. Researchers interested in obtaining additional information about these materials may contact the corresponding author at chris@matchstickllc.com.

Ethics Statement

All study procedures were conducted in accordance with the Declaration of Helsinki and its subsequent revisions. Written informed consent was obtained from all participants prior to enrollment for publication of anonymized images and video stills of their infusion equipment, supplies, and processes. This was a non-interventional, observational study as described in the United States 45 CFR 46.104(d)(2) and all required criteria were met for exempt research under this policy.

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The authors would like to sincerely thank the study participants for sharing their infusion practices and personal experiences with the research team. All product names and brands are the property of their respective owners, and any mention of specific companies, products, or services used in this manuscript are for identification purposes only. Use of these names does not imply endorsement. James Hawthorne's current affiliation is Sobi North America, Waltham, MA, USA; Dimos Katsaros' current affiliation is Kiniksa Pharmaceuticals, Lexington, MA, USA.

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Disclosure

Dr Chris Franzese reports grants from SHL Medical during the conduct of this study; in addition, Dr Franzese has a patent US20230372610A1 pending to Assignee: SHL Medical, a patent US20230226272A1 pending to Assignee: SHL Medical, a patent US20230390483A1 pending to Assignee: SHL Medical, a patent WO2024217896A1 pending to Assignee: SHL Medical, and a patent WO2024042040A1 pending to Assignee: SHL Medical. Dr James Hawthorne reports grants from SHL Medical during the conduct of this study; in addition, Dr Hawthorne has a patent WO2024042040A1 pending to Assignee: SHL Medical. Dr Dimos Katsaros reports grants from SHL Medical during the conduct of this study. Mr Marty Coyne reports grants from SHL Medical during the conduct of this study; in addition, Mr Coyne has a patent US20230372610A1 pending to Assignee: SHL Medical, a patent US20230226272A1 pending to Assignee: SHL Medical, a patent US20230390483A1 pending to Assignee: SHL Medical, a patent WO2024217896A1 pending to Assignee: SHL Medical, and a patent WO2024042040A1 pending to Assignee: SHL Medical. The authors report no other conflicts of interest in this work.

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