



Supporting patients with unlicensed medicine use: Analysing the script schemas for prescribing, pharmaceutical assessment and supply

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ABSTRACT

Unlicensed medicines (ULMs) are those which have not received authorisation from a regulator, as such they do not have the same reassurances around safety and efficacy as licensed medicines. This study aimed to explore the use of ULMs from the perspectives of prescribers, pharmacists and patients within the UK National Health Service (NHS) setting.

Grounded theory was used as a framework, conducting 28 semi-structured qualitative interviews with prescribers, pharmacists and patients across both primary and secondary care settings. Participants were identified from their known use of ULMs where possible and a theoretical sampling approach was used to support recruitment of participants based on the emergent analysis. Analysis followed a constructivist inductive approach, using constant comparison to develop initial themes. This was followed by two focus groups, one with patients and one with professionals where initial analytic findings were presented to participants to further support the development of themes. All interviews were audio recorded and transcribed verbatim.

Three sequential schema scripts were identified and used as a framework to explain our findings: ULM prescribing, pharmaceutical assessment of an ULM and ULM supply. Common and divergent events within these scripts were identified and analysed in an attempt to explain similarities and differences across primary and secondary care and between actors. The analysis identified issues around healthcare professional awareness of using ULMs, perceptions of ULM safety, challenges around what information should be provided to patients and by whom and adds to the debate around the place of ULMs in treatment pathways. This study highlights the need for a multidisciplinary conversation about how ULMs should be used in the NHS.

1. Background

An unlicensed medicine (ULM) is a medicine which does not have the relevant authorisation from the designated healthcare regulator.¹ In the UK, this is the absence of a Marketing Authorisation (MA) from the Medicines and Healthcare Regulatory Agency (MHRA). The European Medicines Agency (EMA) labels ULMs as 'unauthorised medicines'² and the Food and Drug Administration (FDA) refers to ULMs as 'Pharmacy Compounding'.³ In all jurisdictions, the use of such medicines is permitted where existing authorised medicinal products are not able to meet the specific needs of the patients.² This could be due to the lack of a liquid formulation, for example for a patient with swallowing difficulties, but also could include products with an Active Pharmaceutical Ingredient (API) which is not approved for use in the regulators' country. This commonly incorporates

products with an API which may pre-date the existence of the country's authorising body, but also products which have been approved in other nations but not adopted in the individual country. Due to the country-specific nature of ULMs, the actual products which are included in this category vary. A list of 649 ULMs in use were identified in the NHS at the time of writing (March 2021).⁴ Previous research highlights that ULMs are associated with increased adverse reactions.⁵ Concerns about the quality of ULM manufacture⁶ have led to increased regulation of this process in the US,⁷ and this is mirrored in UK.⁸ This regulation has led to ULMs attracting higher costs in the UK NHS but in the EU, there have been concerns that ULMs have offered a cheaper but more risky alternative to licensed products.⁹ However, this regulation relates to the quality of the product only. The products still do not have a MA as an endorsement that ULMs are safe and effective, so the absence of this can make decision making

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around their use problematic for clinicians.⁴ This also means that guidance on their use centres around clear communication with patients about the risks and benefits of using such medicines.

The lack of a MA for ULMs also results in a reluctance for their recommended use at a national level in the UK, by bodies such as the National Institute for Health and Clinical Excellence (NICE). General guidance on their use and best practice recommendations have been produced by the General Medical Council (GMC)¹⁰ and Royal Pharmaceutical Society (RPS) in the UK.¹¹ Work conducted by us has analysed the content and quality of guidance documentation available on ULM use within individual healthcare organisations in the NHS.¹² Substantial inconsistencies between guidelines were identified resulting in a lack of clarity on how decisions about ULMs are made. Therefore, we identified that exploring this qualitatively would be beneficial to understanding how ULMs are used within the NHS.

The concept of 'schema' was first posited by the child development psychologist Jean Piaget who employed the concept to explain the development of learning in children.¹³ A schema can be defined as a set of linked mental representations of the world, which are used to both understand the world and to respond to situations in it. Schema (or schemata) are stored and applied when needed. New information and experiences are compared to existing schema which can be modified.¹⁴ The process of receiving new information and incorporating it into schemas continues until equilibrium is reached i.e. a state of cognitive (mental) balance. This equilibrium is maintained until additional information is received. Thus, schemas are shaped by learning and new experiences. Schemas have previously been used as a framework to describe prescribing decision making by medicals¹⁵ and patients' perspectives of medicines.¹⁶

It was suggested by Schank and Abelson¹⁷ that schemas can also be further subdivided into scripts, goals and plans. Scripts are made up of individual events or actions. Scripts can also be personalised to the individual, who may change the events in their own script whilst still acknowledging a common script that most people will understand. Scripts exist from the perspective of one particular 'actor' (in this paper we will call them the script 'owner') but may involve multiple actors. In this paper, the schema represent actors from both primary and secondary care and include prescribers (both medical and non-medical), pharmacists and patients. Each script is different depending on the different actors' point of view but a 'whole view' of a script can be created by considering a combination of these scripts together. In this paper, script schema is used as a framework to understand the scripts and events associated with ULM use from the perspectives of different actors. It is important to note that the aim of this approach was not to determine whether ULMs should or should not be used, but to explore *how* they are used within the UK NHS.

1.1. Aim

To create a model which describes the use of ULMs from the perspective of prescribers, pharmacists and patients across primary and secondary care settings.

2. Methods

2.1. Design

A qualitative method was employed to allow for an open exploration of ULM use in current practice. A constructivist grounded theory approach¹⁸ was used. This approach places emphasis on the phenomena which are being studied and considers that both the data and the analysis of that data are created from the experiences shared amongst the researchers and participants and the relationships that exist within and between these. Emphasis is placed upon how participants construct meanings and perform actions in certain situations. It goes beyond describing how participants view their situation by theorising both the interpretive work that participants do and recognising that the researchers' explanation is itself an interpretation. Constructivist grounded theory moves beyond the purely descriptive by combining themes from the data, the things participants do and say, and

using them to construct higher order theories to make sense of actors' meanings and behaviours. Our higher order theory was to use schema scripts.

2.2. Sampling

The sampling frame for the study focused on the actors who made decisions about the use of ULMs. This included the prescribers who initiate ULMs, pharmacists who procure the ULMs and patients who take (or not) the medicine. Purposive sampling was initially used to select one participant from each of these actor groups separately for both care settings. Theoretical sampling was used following initial analysis of the data to identify participants who could corroborate or provide divergent views in relation to the emergent themes. This was done across both work strands through regular discussions between GD and LP.

The inclusion of off-label medicines was not originally planned. However, we found that participants in both the patient and healthcare professional (HCP) groups frequently confused off-label prescribing with ULMs. Therefore, it was felt that the data captured both elements. For ease, we will refer to ULMs throughout this paper.

2.3. Data collection

Two methods of data collection were employed. First, face-to-face semi structured interviews were conducted with participants between June and November in 2015. Topic guides were developed based on the aims and objectives of the study and previous work on an ULM guideline analysis. Three versions of the topic guide were developed, one for each participant group (prescribers, pharmacists and patients). The guides used were common to both primary and secondary care but evolved based on the emerging analysis for each strand as per the principles of a constant comparison approach.¹⁹ Interviews were conducted by GD and LP. Copies of these topic guides are available in the supplementary materials. As we expected the topic guides to change as data collection and analysis progressed, we did not pilot these prior to use. Interviews took place in a location and space agreed upon with the participant. This was most often within consultation rooms in general practices and office space in secondary care, but also patients' homes. No additional persons were present beyond the participant and the researchers in any of the interviews. Each participant was only interviewed once.

After initial data analysis using the grounded theory approach, findings were presented to participants in two focus groups, one for patients and one for HCP participants. The focus groups took place in February 2016 and were led by GD with support from LP. A topic guide for both focus groups was developed based on an interim analysis, to share the themes which had been identified. Sense checking theories from the analysis with actors is a common technique of the constructivist grounded theory approach, in order to confirm researchers' understandings and explanations.²⁰

Interviews and focus groups were audio recorded and transcribed verbatim prior to data analysis. Transcripts were not returned to participants prior to analysis due to project time constraints. Rather, focus groups were used as an opportunity for participants to comment on the emergent findings. Field notes were also made by both researchers following interviews to capture any additional data relating to the study.

2.4. Data analysis

Transcripts from both the interviews and focus groups were used as the primary data for analysis. Initial inductive coding was undertaken by GD for the primary care strand, and LP for the secondary care strand. Constant comparison between the data and codes from both strands, combined with regular discussions between GD and LP allowed for analytic refinement and agreement of joint and divergent codes to identify genuine differences between the strands. This discussion also facilitated agreement that data saturation had been reached at the end of the study. Final consolidation of codes across both strands was led by GD with input from LP. Findings based on the identified themes from the secondary data analysis were

considered reflexively by the study authors in relation to potential social or psychological theories. This led to the use of the script schema to support the explanation of the results. NVivo 11²¹ was used to facilitate the analysis process.

2.5. Participant recruitment

For interviews, HCPs in secondary care were recruited via email in one NHS hospital trust in North East England. Prescribers issuing ULMs were identified prior to sampling. All pharmacists working within the trust were considered within the sampling frame. Patient participants were identified during out-patient clinics where ULMs were prescribed with the permission of the prescriber for that clinic.

Primary care participants were recruited across the region of North East England for interview. It was assumed that all HCPs would have had some experience with ULMs given the high prevalence of prescriptions within this setting. Recruitment of HCPs was via emails through professional networks of GD. Patients were identified from general practice records as prescribed an ULM and recruited via a letter. All participants who had participated in an interview were invited to attend the relevant focus group.

The researchers did not have any prior relationship with patient participants, but often had a relationship with HCPs recruited through professional networks. Participants received an invitation letter from the research team and a participant information sheet for both the interviews and focus groups. In these materials all participants were informed of the study aim, with patient participants being informed that they had been identified as a suitable participant as they were prescribed an ULM. Secondary care prescribers were also informed that they had prescribed an ULM. It was made clear in participant information sheets for pharmacists and prescribers that we were not seeking to judge the use of ULMs, but to explore how they are used and therefore avoid participants feeling that they were under any form of scrutiny. Healthcare professionals were not provided with any incentive to participate in the research, but patients were provided with a £20 voucher as a 'thank you' for their time both for the interview and attendance at the focus group. Consent forms were provided to all participants to return to the research team prior to arranging data collection. This was done for both the interview and focus group elements of data collection. The number of invitations to potential participants was not able to be collected. For patients, we did not have these figures as we did not directly contact patient participants as they were approached instead by their prescriber or GP practice. For professionals, we did not keep a tally of invitations through professional networks as we often used group emails. Thus, non-participation for primary and secondary care could not be determined.

2.6. About the researchers

GD and LP are both female pharmacists, working in joint roles within academia and the NHS. GD within an NHS commissioning organisation and LP in an NHS hospital setting. Both undertook training in qualitative data collection and analysis prior to the study. GD also had previous experience of qualitative research methods.

2.7. Ethical approvals

The study was given a favourable opinion by Yorkshire & The Humber - Leeds West Research Ethics Committee (Reference 17/YH/0191) and approved by the University of Sunderland.

3. Results

Twenty-eight participants were recruited to the study. Seven were patients and 21 were HCPs. HCPs included community pharmacists ($n = 3$), general practice pharmacists ($n = 2$), General Practitioners (GPs) ($n = 5$), secondary care prescribers ($n = 6$) and hospital pharmacists ($n = 5$). The sample characteristics for healthcare professionals can be found in

Table 1

Summary of demographic characteristics for healthcare professional interview participants.

Demographic information	Interview participants (N)
Healthcare professional years of experience	
Prescribers	
Newly qualified (up to 5 years)	2
Mid-career (6–20 years)	3
Late career (21+ years)	6
Pharmacists	
Newly qualified (up to 5 years)	4
Mid-career (6–20 years)	3
Late career (21+ years)	3
Healthcare professional specialties	
Generalist (including newly qualified)	13
Paediatrics	2
Haematology	2
Ophthalmology	1
Surgery	1
Diabetes	1
Pain	1
Healthcare professional gender	
Male	11
Female	10
Prescriber professional background	
Medical	8
Nursing	2
Pharmacist	1

Table 1 and for patients in Table 2. The average length of an interview was 44 min, with interview times ranging from 18 min to 74 min.

Additionally, four people ($n = 1$ community pharmacist, $n = 2$ hospital pharmacists, $n = 1$ secondary care prescriber) attended the focus group for HCP participants lasting 74 min. Three individuals attended the focus group with patients which lasted 33 min.

Analysis identified schema scripts describing three sequential stages associated with ULM use. These were: prescribing an ULM (Stage 1), pharmaceutical assessment of an ULM (Stage 2) and supply of an ULM (Stage 3). These sequential scripts were identified through data analysis from all participants from both the interviews and focus groups. Script compilation revealed commonalities as well as discrepancies between actors on the events making up each of these scripts.

Table 2

Summary of demographic information for patient interview participants.

Demographic information	Interview participants Age (Years)
Patient age ($n = 6^a$)	
Mean	48
Range	21–67
Demographic information	Interview participants (N)
Patient role	
Patient	6
Carer	1
Patient gender	
Male	1
Female	6
Patient recruitment setting	
Primary care	5
Secondary care	2
Patient medicine category	
Neurology	2
Dermatology	2
Pain	2
Gastroenterology	1

^a Age information unavailable for one participant.

3.1. Prescribing of ULMs Script

The first stage of ULM use is described in the prescribing of ULMs script as seen in Fig. 1. The owners of this script are prescribers. Outside actors have also provided data on this script from their perspectives. Some events are only present in either primary or secondary care and these are noted using protruding arrows. Events within the script are also classified as either: agreed amongst all actors, inconsistently described amongst actors or expected by outside actors but not the script owners. The events have been organised in an order similar to that described by our participants, however this is not fixed and the timing of events could be variable.

3.1.1. Receive prescribing request from secondary care

Receiving a request from secondary care to prescribe an ULM was a unique event to participants from primary care as part of the prescribing of ULMs script. There were mixed feelings about the transfer of care for ULMs, often due to the unfamiliarity of primary care prescribers with these medicines.

"I think the shift from hospital to community is just fraught with possible mistakes. Because you're asking people who don't use that medicine to prescribe that medicine when they may not be au fait with that medicine." General Practitioner 3, Interview.

3.1.2. Apply for ULM to be on local formulary

In secondary care, participants described applications for ULMs to appear on the local formulary as a pre-requisite for prescribing an ULM.

"I had to liaise with our pharmacy to say this was a specific preparation that I was going to want to continue giving. For these reasons, I had to justify it. I think I went to our pharmacy group, or prescribing group within the Trust, to check that people thought it was reasonable." Secondary Care Prescriber 6, Interview.

3.1.3. Recognition of the ULM

Recognising an ULM was an event that was identified by all participants as important to the subsequent use of ULMs. However, there were mixed reports in the data about how often this event formed part of prescribers' scripts. GPs, less experienced doctors and nurse prescribers reported that they were not always sure when they were prescribing an ULM. This lack of awareness was often attributed to prescribing systems not necessarily alerting them to the medicines' status.

"So if it comes up and you're maybe a newly qualified doctor, or a GP registrar, you'd just think, 'well, if it comes up when I type it in, it must be alright to use, because it's on the system', without realising what it's licensed in or not..." General Practitioner 1, Interview.

3.1.4. Establish the cost of the ULM

In primary care, an event to establish the cost of the ULM did not appear in data collected from secondary care. Primary care prescribers seemed to have a heightened awareness of ULMs being high cost and this was sometimes found to be a source of conflict when attempting to transfer care for patients receiving ULMs. Patients were also aware of costs in relation to the prescribing of ULMs script.

"I know one of the medications that [my daughter] was on, the Acetazolamide, which just this year we couldn't get the tablet form so we ended up having to get the liquid form, but that was very expensive and obviously the doctor was a bit reluctant to give her it." Primary Care Patient 1, Interview.

3.1.5. Considering all available treatments

All prescribers described the consideration of all available treatments to meet patient need. It was consistently agreed that a licensed medicine should always be used in preference to an ULM. However, once a licensed medicine was unable to meet the needs of the patient, the choices which came next in terms of preference were unclear. There was also evidence of some ULMs being used as part of established practice, and this led to less emphasis on considering a large range of alternative treatment options. The patients' over-riding concern was that they were not comfortable being used as a "guinea pig", and therefore felt that the prescriber should have some experience which supported the selection of an ULM.

"You've reached the end of what is licensed or perhaps what is you know the clinical first, second, third line agent and you're left with little or no choice really." Secondary Care Prescriber 2, Interview.

3.1.6. Seek further information about the use of the ULM

Ensuring that prescribers had all the relevant information to safely prescribe ULMs was common to primary and secondary care scripts. However, most prescribers acknowledged that this could be difficult, especially in primary care where information available might be limited. Primary care prescribers often relied on information provided by secondary care clinicians who were often the source of the prescription request. In secondary care,

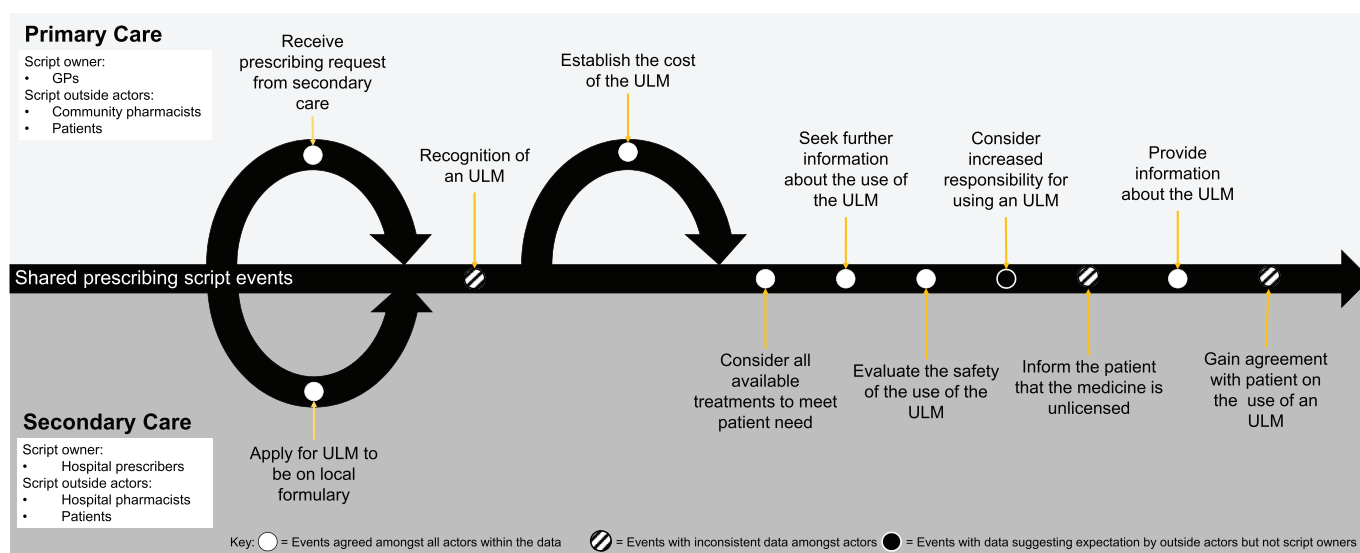


Fig. 1. Diagram representing schema script events for Stage 1: Prescribing an unlicensed medicine (ULM).

experienced clinicians described using research literature or experience of colleagues as sources of further information.

"If it's a special then I'll either have to look it up in the BNF and often the instructions get very vague. So often when it's unlicensed or it's just really special, they'll often have very, very vague instructions. Or no instructions and they'll simply list it. In which case then I know I need to find out more." General Practitioner 3, Interview.

3.1.7. Evaluate the safety of the use of the unlicensed medicine

Most prescribers acknowledged that the safety profile for ULMs was different to that of a licensed medicine and evaluating the safety for the use of an ULM was a distinct event. However, prescribers generally perceived that ULMs were safe. This opinion seemed to be based on a lack of reports from patients that any adverse events had occurred. Some prescribers however, reflected that this perception might change if they did have a patient who experienced harm from an ULM. Safety was a primary concern of the patient participants, although all trusted the judgement of their prescribers.

"Well, at first, it was only when I read all this I think, I just sort of thought 'oh, are they testing it?' That was my first thought. Is it still sort of not one hundred percent safe? Has it been tested? That was all. But I wasn't unduly bothered or anything. I'm not that type of person you know." Primary Care Patient 3, Interview.

3.1.8. Consider increased responsibility for using a ULM

When considering the implications of using an ULM, most pharmacists highlighted the increased responsibility that prescribers attracted in the absence of a MA being in place. They expected that this was considered as part of the prescribing an ULM script. However, prescribers themselves often did not differentiate their liability for prescribing ULMs and that of licensed medicines. Therefore, this was an event which was expected by pharmacists but not included in prescribers' script.

"I think if something is used a lot and is within recognised medical practice then I don't think I worry about the fact that it's unlicensed any more than something being licensed, because I don't think it really matters to be honest." General Practitioner 5, Interview.

3.1.9. Inform the patient that the medicine selected is unlicensed

Most prescribers intended to inform their patients that their medicine was unlicensed as part of a shared decision-making process. Patients and pharmacists also expected that this should be an event in the prescribing of ULMs script. However, prescribers' lack of awareness of which medicines were unlicensed was a barrier to including this event in their scripts. Some prescribers were reluctant to inform patients, including one who actively chose not to inform their patients.

"...if we have some with side effects then I would say this and this side effect. That's important, the fact that it's unlicensed or licensed is not important." Secondary Care Prescriber 6, Interview.

For patient participants, those recruited from secondary care reported being informed that their medicine was unlicensed as part of the prescribing script, however none recruited from primary care had been informed although all had their ULM initiated by a hospital prescriber. All patients however, felt that this should be an event as part of the prescribing script.

"I think I would have liked to have known it was unlicensed. I didn't know until you told me. I still don't think I would have been worried about it though..." Primary Care Patient 4, Interview.

3.1.10. Provide information about the unlicensed medicine

Within the data, prescribers in both primary and secondary care reported endeavouring to provide patients with information about their medicines. The content of this information generally included the indication of

the drug, potential side effects, length of treatment, expected treatment outcomes and how to use the medicine. For prescribers, there was generally no perception of difference between this event as part of prescribing an ULM script and their equivalent script for licensed medicines. Many prescribers felt that they would benefit from providing written information about what an ULM was, however, could not identify a source for this.

"It was more just what will happen when you use it because it's obviously quite an unusual use, and the side effects of it. ...So that was the counselling that they gave." Primary Care Patient 5, Interview.

3.1.11. Gain agreement with patient on use of the unlicensed medicine

Where prescribers were happy to inform patients that their medicine was unlicensed, this was linked to another event where they would gain agreement for using an ULM with the patient. Some patients also reported positive experiences of shared decision making with their prescribers.

"I do believe the consultant actually said to me 'go home, have a look at it, next appointment we'll see.' So I went away, did a bit of research and I thought the uses of, in a controlled situation, I thought 'well, the least I can do is give it a try'" Secondary Care Patient 2, Interview.

3.2. Pharmaceutical assessment of ULMs script

The second stage of using an ULM described by our participants is represented by our pharmaceutical assessment of an ULM script as shown in Fig. 2. The owners of this script are pharmacists working in either community pharmacy, general practice or secondary care. Whilst this script was a precursor to the supply of ULMs script for hospital and community pharmacists, GP pharmacists used this script as part of medication reviews.

3.2.1. Recognition of the ULM

Although recognition of an ULM event was present in both primary and secondary care, community pharmacists reported being able to quickly recognise an ULM. Hospital pharmacists based on wards cited their removal from the dispensing process to conduct clinical work on wards meant that they were less aware of which medicines were unlicensed.

"Generally in the computer system, if you do a stock enquiry if it's unlicensed it would just have a code UNL on the stock code, so you would know it that way. But when you look at it on the paper order, you don't." Hospital Pharmacist 2, Interview.

3.2.2. Speak to the patient to gather information about the use of the ULM

Speaking to the patient was an important event for community pharmacists in order to gather information about ULM use as part of their pharmaceutical assessment of the ULM script. Patients provided information about their use of the medicine and allowed an assessment of what information the patient knew. This could then be used to tailor the provision of information event as part of the ULM supply script.

"I would maybe just go out and advise them. Have they had this before? Do they understand what it's being used for?" Community Pharmacist 2, Interview.

3.2.3. Check formulary status of the ULM

In secondary care, checking the status of an ULM on the local formulary was a unique event for hospital pharmacists. This enabled assessment of likely availability of the ULM and provided information about how their hospital categorised the risk of the ULM.

"If it's an unlicensed preparation we do a risk assessment in the first place. The simple things like is the label in English. Have we got the certificates of analysis or certificates of conformance if it's made in the EU. We also look at the packaging, for the directions if they want supplementary information. So those are the types of things that we look at." Hospital Pharmacist 1, Interview.

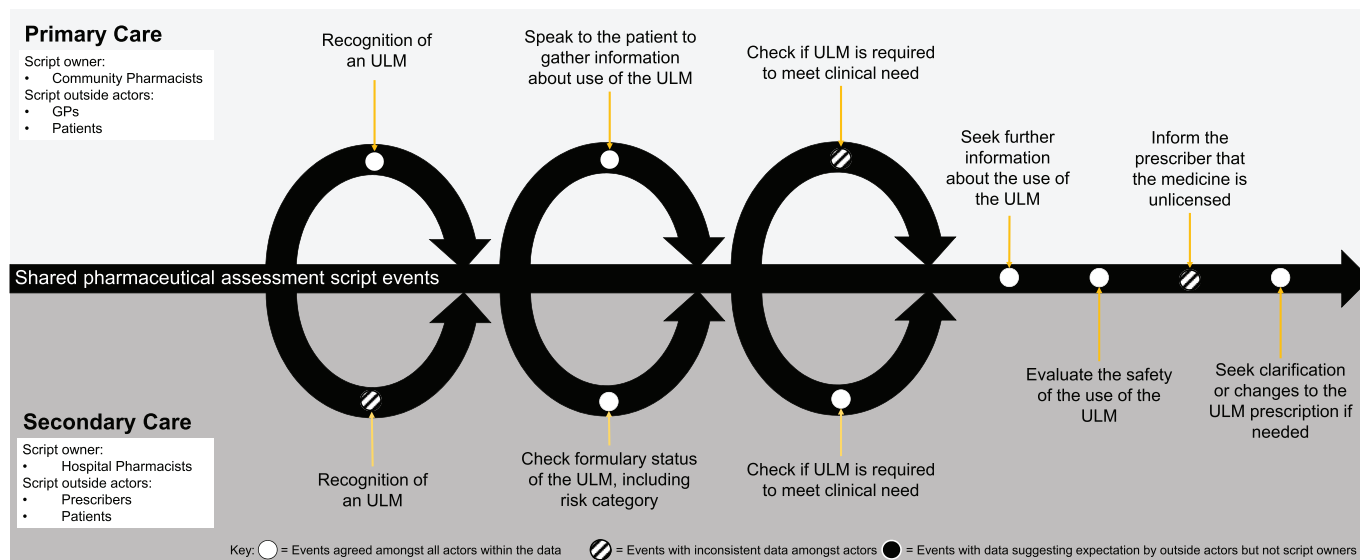


Fig. 2. Diagram representing schema script events for Stage 2: Pharmaceutical assessment of an unlicensed medicine (ULM).

3.2.4. Check if an ULM is required to meet clinical need

An event to check if an ULM was required to meet clinical need was common to both primary and secondary care, however this event appeared less consistently amongst community pharmacists. In common with prescribers, hospital pharmacists and general practice pharmacists described a wide range of potential alternatives to using an ULM with a preference for using a licensed medicine first. Amongst pharmacist participants however, there was more consistency for considering off-label uses of licensed medicines as the next best alternative to an ULM. One GP pharmacist who also had experience working as a community pharmacist highlighted the challenges of performing this event in the community pharmacy setting. In particular, time available and access to specialist resources.

"I can honestly say I don't know any community pharmacists that would proactively look at someone who's taking a special and think 'oh, should we try and change this?'" GP Pharmacist 1, Interview.

3.2.5. Seek further information about the use of the ULM

Pharmacists across primary and secondary care reported seeking further information about ULMs as part of the pharmaceutical assessment script. Pharmacists generally reported accessing a wider range of resources to support their decision making compared to prescribers in the equivalent event as part of the prescribing an ULM script.

"...probably first I would try the BNF. If it's something like a monoclonal antibody or something a bit more exotic that's not going to be in the BNF, then I would either have a look in Martindale or probably look up the [Summary of Product Characteristics]" Hospital Pharmacist 5, Interview.

3.2.6. Evaluate the safety of the ULM

For all pharmacist participants, evaluating the safety of an ULM was a key event with the pharmaceutical assessment of an ULM script. However, in addition to the acknowledged lack of safety information reported by prescribers, pharmacists also considered risks in relation to the formulation of the ULMs. Pharmacists often contextualised ULMs as 'adaptations' of licensed medicines.

"Most of the specials that we deal with are just a variation on something that is licensed and they just realise it's done slightly differently." Community Pharmacist 1.

3.2.7. Inform the prescriber that the medicine is unlicensed

There were mixed reports amongst pharmacists about whether routinely informing the prescriber that the medicine was unlicensed was an event as part of the pharmaceutical assessment script. Most described making a judgement about whether the prescriber was likely or not to know that the medicine was unlicensed based on the frequency with which the ULM was used and their knowledge of the prescriber themselves. However, most prescribers felt that this was something that should happen.

"I think it's important that the pharmacist[s] let us know. They say, 'wait a minute this is unlicensed'." General Practitioner 2, Interview.

3.2.8. Seek clarification of changes to the ULM prescription if needed

Where issues arose as a result of the pharmaceutical assessment script, pharmacists described an event where they would either seek clarification that the prescriber intended to use an ULM or suggest changes to the ULM prescription. Prescribers also described these interactions. Some pharmacists felt that prescribers saw these conversations as an inconvenience, but there was also evidence that these were valued.

"They double check things and they ring you up if they're unsure, or if you've made an error they'll check it, and they'll come back to you with that. So there's always that safety net as well, and even if they pick up on something, then you think 'well actually, I'll not do that again.'" Secondary Care Prescriber 4, Interview.

3.3. Supply of an ULM script

Stage 3; supplying an ULM (see Fig. 3). With script owners being community and hospital pharmacists.

3.3.1. Select supplier for the ULM

Selecting a supplier for the ULM was an event shared by primary and secondary care, but with discrepancies. Community pharmacists working for national pharmacy multiples for example, had a set ULM supplier selected for them by a head office organisation. However, community pharmacists working for independent and smaller companies reported having a preferred supplier but could use others if they felt they needed to. This flexibility could be used to meet either commercial or patient interests. When asked about what made a supplier favourable, community

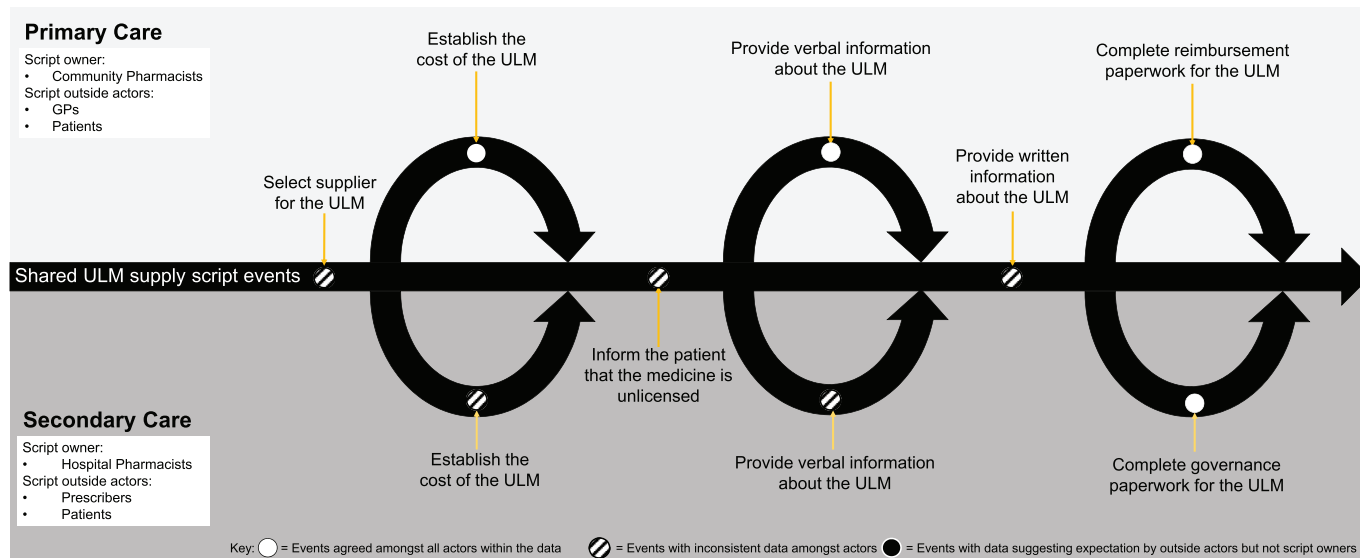


Fig. 3. Diagram representing schema script events for Stage 3: Supply of an unlicensed medicine (ULM) to the patient.

pharmacists placed an emphasis on customer service. In secondary care however, hospital pharmacists relied on centralised processes for supplier selection. One hospital pharmacist described systems in place to evaluate suppliers on a case-by-case basis.

“When the [ULM provider] representative calls I will go through, what is it that you do, what's your background, how big is your company? How long has it been trading? What sort of preparations do you make and can you give me an idea of your facilities that you've got? To try and build up a picture and it may be that sometimes we want to go out and visit them.” Hospital Pharmacist 1, Interview.

3.3.2. Establish the cost of the ULM

Establishing the cost of the ULM was mentioned as an event by most community pharmacists and reflects the event in the prescribing of ULMs script in primary care. As predicted by our GP pharmacists, community pharmacists did not report contacting prescribers to seek an alternative product based on higher costs. Establishing the cost of the ULM was not described consistently as an event amongst hospital pharmacists. Data from participants suggested that this would only be considered in secondary care if there were multiple ULMs required by a patient.

“...when I'm on the ward where they're deciding to switch an old lady who can't swallow or whatever onto a load of liquids or something like that, then I do think about cost a little bit.” Hospital Pharmacist 1, Focus Group.

3.3.3. Inform the patient that the medicine selected is unlicensed

Provision of medication counselling by pharmacists is a common element of medicines supply. In the case of an ULMs however, there was much debate amongst participants about whether informing the patient that their medicine was unlicensed was part of the ULM supply script. There were mixed opinions from pharmacists, with many reporting uneasiness about having this conversation with patients.

“I would have expected the doctor to be explaining this, especially as it's quite unusual for them to be prescribing it. I would imagine they would have got a much more thorough explanation from the GP.” Community Pharmacist 3, Interview.

Prescribers also expressed discomfort about pharmacists informing patients that the medicine is unlicensed as part of the medication supply script.

“...would the pharmacist necessarily tell them? Because the pharmacist wouldn't know what they're getting it for. They don't know the indication, they just know what the drug is being given.” General Practitioner 1, Interview.

Patients also expressed a preference for this step to be included in the prescribing of ULMs script rather than the medication supply script.

“... I would expect the person prescribing to explain to me what that it is. I don't think I would expect it from the pharmacy....” Primary Care Patient 2, Interview.

3.3.4. Provide verbal information about the ULM

Pharmacists in community pharmacy agreed that providing verbal information to patients was part of their ULM supply script. However, the content of this information differed from that in the prescribing script. Providing information in the medication supply script typically included: lag time for the ULM to be available for collection, availability of information about the ULM, manufacturing of ULMs, potential for reduced shelf-life, special storage conditions, and the liability for adverse drug reactions resting with the prescriber rather than the manufacturer. Hospital pharmacists however, did not always describe providing verbal information about ULMs to patients as part of their ULM supply script.

“If there's a short self-life on the products, that kind of thing, different storage things. I make a big deal of making sure the patient knows about them because you don't want the products wasted.” Community Pharmacist 3, Interview.

3.3.5. Provide written information about the ULM

There was an expectation from prescribers that pharmacists would provide written information about ULMs as part of the ULM supply script. However, pharmacists described difficulties in fulfilling this event as part of the script. This included difficulties where imported ULMs came with information in a foreign language or where an ULM had been manufactured and a leaflet was not supplied. Patients also reported not receiving written information about their ULM.

“... [The ULM is] Canadian and it's in French, and English, but there is no ingredients on it or a leaflet with anything, it's just a bottle.” Patient Participant, Focus Group.

3.3.6. Complete paperwork

Completing paperwork was an event in the ULM supply script for pharmacists in both primary and secondary care, but each with a different focus. The purpose of the paperwork in secondary care was to quantify risk associated with use of ULMs and highlight this to the prescribers. However, some saw this as more of a bureaucratic process. The paperwork in primary care seemed to relate primarily to reimbursement.

"My personal thing is not so much is it clinically appropriate, it's is all the paperwork correct and available and filled in." Hospital Pharmacist 5, Interview.

4. Discussion

This study is the first study that we know of to investigate the use of ULMs within the NHS using the perspectives of prescribers, pharmacists and patients across both primary and secondary care settings. This approach has allowed us to compile a comprehensive system overview using data which can be categorised according to schema scripts. The scripts have provided useful insights into the events which make up the use of ULMs. This includes how the different actors interact with each other and their perceptions of theirs and others' roles in the use of ULMs.

To develop ULM schema scripts, pharmacists and prescribers need to be taught what an ULM is. Only pharmacists in our data were generally able to correctly define an ULM. This may be due to a greater emphasis on drug manufacturing and legislation as part of their core training, however our less experienced pharmacists were still less confident about these definitions and this is reflected in other work.²² Another paper has also highlighted the potential for confusion surrounding the use of unlicensed and off-label use of medicines.¹ In the UK, the GMC has further complicated the issue by combining both off-label and ULM within the same guideline¹ despite the guidance note from the MHRA making clear differentiations in risk between these two categories.²³ In a previous analysis of 52 guidance documents for ULMs, 23 different versions of terminology were used to describe these medicines so it is unsurprising that HCPs find these definitions difficult to understand. Non-medical prescriber participants in our study noted that they were initially not permitted to prescribe ULMs, and therefore teaching about these had been omitted from their original training with no updates or additional training offered subsequently. Consistent definitions are needed to better support comprehension of terminology associated with ULMs across healthcare professionals.

Knowing that a medicine is a ULM is also important. Hospital pharmacists' awareness of using an ULM was limited compared to community pharmacists, who had additional supply script events in their schema. The prescribers in our sample working in paediatrics and ophthalmology described routine use of ULMs and were more aware of when they were being used. To date, most research around ULMs has centred on their use in paediatrics^{2,24,33,25–32} and the EMEA has written specific guidance about safety considerations in this patient group³⁴ and so they are likely more familiar with ULMs, and also that many more medicines are used off-label in this patient group. Clinical speciality has been suggested to influence the formation of schemas in relation to prescribing by others.¹⁵

Once it has been established that an ULM is being used, it is then important to consider how this potentially changes the use of the medicine. In contrast to our pharmacists who clearly articulated the lack of MA as putting both the prescriber and the supplying pharmacist in a greater position of responsibility, prescribers did not differentiate ULMs and licensed medicines in their clinical decision-making process. The GMC have also implied that prescribing unlicensed and off-label medicines does not put prescribers' registration at any greater risk,¹ and therefore there is a clear discrepancy in message about the risk that prescribers take on when using these medicines.

Consideration of safety is clearly an important part of this risk assessment. This was present in all three of our scripts and from all perspectives. In the UK, ULM manufacturers report adverse reactions to the MHRA.³⁵

Pharmacists and prescribers also report ADRs via the Yellow Card Scheme.^{11,23,36} However, data for the MHRA Yellow Card Scheme is only published by API without associated formulation, so ULMs and licensed medicines cannot be differentiated in the data. A lack of evidence for ULM safety has been highlighted by other research,³⁷ where patient registries have been suggested as a way of capturing adverse events to better support understanding of their safety. Assessment of risk is also included in guidance published by the RPS.^{11,36} In particular, the RPS highlight the lack of information clinicians have available to make informed decisions about prescribing ULMs. Potential pharmaceutical issues with ULMs have also been highlighted by others.²² However, risk perception by individuals is influenced by an availability bias; most participants in this study could not describe a significant adverse consequence from using an ULM and this can create biases in the formation of schema.³⁸ This combined with the absence of robust data could lead to the conclusion that ULMs are safe to use.

Risk of ULMs also needs to be weighed against potential benefit. The pharmaceutical assessment of ULMs script described reflects the principles of pharmaceutical care first described by Hepler and Strand,³⁹ where the objective is to ensure the best outcomes for patients from drug therapy. There was much debate about the place of ULMs in treatment pathways. This assessment was hampered by the information deficit for ULMs. Patients were grateful for the opportunity to try something that they found to be effective, and specialist prescribers were very comfortable using ULMs as part of routine practice. It has previously been found that guidelines attempting to place ULMs within a treatment pathway did not agree, making the place of ULMs still unclear. Speciality specific guidelines have previously been identified on the use of ULMs including in ophthalmology⁴⁰ and dermatology⁴¹ and NICE have also started producing evidence summaries for ULMs.⁴² More guidelines for use of ULMs could support healthcare professionals to make better judgements on the place of ULMs within treatment pathways and support the development of formularies of ULMs. Formularies have been recommended by others as another way to oversee the use of ULMs^{11,43} and was highlighted as valuable by participants in our schema scripts.

Use of ULMs is also based on a cost-effectiveness decision. Awareness of the cost implications of using ULMs was present only amongst those actors present in the primary care setting. Higgins and Tully¹⁵ also found that cost is of little consideration to prescribers working in secondary care when making prescribing decisions. Pharmacists working in general practice reported costs in their pharmaceutical assessment script and this is likely due to prescribing budget management being part of their role.⁴⁴ We have previously highlighted the increased cost associated with ULMs⁴⁵ however there remains some debate about what impact this should have on their use.

On a more practical level, ULMs also pose some challenges that our work also highlights, the provision of patient information. Prescribers in this study often assumed that written information would be provided by pharmacists as part of the ULM supply script and had little awareness of issues pharmacists faced sourcing information. Patients provided evidence that access to high quality written information about their ULMs was poor and this reflects other studies which have also found lack of information associated with ULMs.²⁵ A national repository of such information would support the more consistent availability of patient facing information across the NHS.

Our 'whole system' approach also allowed us to example how the different care settings worked together to support the use of ULMs. Collaboration across HCP boundaries was present in the data both from pharmacist and prescriber perspectives, including the transfer of ULMs across care boundaries. This importance of good transfer of ULMs is highlighted in guidance for ULMs by the RPS.^{11,36} All our participants highlighted issues around the transfer of care for ULMs and this has been reflected in work by others.²² Primary care prescribers described having a lack of knowledge about ULMs and costs of ULMs were also cited as barriers in prescribing transfer. These issues have also been found in other work done on the transfer of paediatric patients from secondary to primary care.^{25,28}

Central in the data however was the debate around who was best placed to inform the patient that the medicine they were using was unlicensed.

Guidance from the RPS seems to indicate that the responsibility for this should rest with the prescriber,¹¹ therefore in our framework this should be contained within the prescribing script and this position was supported by our participants and has been reflected in work by others.^{32,33} However, given the challenges that prescribers face around awareness of when they are using an ULM, applying this in practice is likely to be difficult. Whilst others have explored pharmacists' perceptions about informing patients about the status of ULM²² or off-label use of medicines,^{29,32,33} we are the first to include this debate from several actors' perspective. We feel that this is something that will need ongoing discussions between prescribers, pharmacists and patients.

4.1. Strengths and limitations

Whilst others have used schemas to illustrate the process of prescribing,¹⁵ we are the first to use this to describe the use of ULMs. We also expand the use of script schema to processes carried out by pharmacists for pharmaceutical assessment and medication supply. This study also used qualitative approaches to capture the delivery of pharmaceutical care and this has previously been highlighted as lacking in pharmacy practice research.⁴⁶ This study adds to the data for the difficulties HCPs face in conceptualising ULMs and how they are used in practice. Many of the schema script events we describe are also reflected by others^{15,22,29} and we feel this adds to their likely transferability.

All qualitative approaches are limited by the self-selection of their participants who choose to be involved in the research. We have attempted to combat this by using a theoretical sampling strategy, where we recruited new participants based on emergent themes. Therefore, we feel have a diverse sample upon which we have based our analysis. No new themes emerged towards the end of our data collection, and therefore we feel that our analysis is likely transferrable to other settings within the UK. We have not found similar studies internationally, so we do not know if these scripts would be transferable internationally. We did only sample from one secondary care institution which may limit some of our findings, specifically concerning governance structures and roles, however, these are still likely to be common amongst most secondary care settings.

5. Conclusion

This work outlines three schema scripts for prescribing, pharmaceutical assessment and ULM supply which sheds light on how ULMs are used within the UK NHS. These scripts highlight the difficulties associated with using ULMs and the assumptions that actors make about the contents of these scripts. Leadership is required across HCPs and patient groups to establish what best practice looks like for ULM scripts and support infrastructure such as training, information, digital traceability and guidance to support their safe and effective use.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Topic guides used in this study this article can be found online at <https://doi.org/10.1016/j.rcsop.2021.100017>.

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