Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials

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Abstract:

Objectives: To investigate the knowledge and views of a range of healthcare professionals (consultant paediatricians, GPs, community pharmacists and paediatric nurses) regarding the use of unlicensed/off-label medicines in children and the participation of children in clinical trials.

Methods: A regional study in which a survey instrument with 39 items was issued to 500 randomly selected GPs, all community pharmacists (n=512), 50 hospital consultants and 150 paediatric nurses in Northern Ireland.

Results: Approximately half (46.5%) of the 1,212 healthcare professionals approached responded to the questionnaire. The majority of respondents indicated their familiarity with the term unlicensed (82.9%) or off-label (58.6%) prescribing with the most frequently quoted reason for such prescribing being younger age (33.6%). Apart from community pharmacists, most respondents reported having gained their knowledge through personal experience. Even though a large percentage of respondents expressed concerns about the safety (77.8%) or efficacy (87.9%) of unlicensed/off-label prescribing in children, only 30.7% reported informing parents/guardians about such use of medicines in children. In addition, only 56% of respondents believed that unlicensed/off-label medicines should undergo clinical trials in children. Overall, 28.4% of respondents (20.1% of GPs, 41.4% of community pharmacists, 27.7% of paediatric nurses and 94% of consultant paediatricians) indicated their willingness to be actively involved in, and recruit their patients for, paediatric clinical research.

Conclusion: The use of unlicensed and off-label medicines remains a major issue in paediatric medicine. Until such times as more licensed medicines are available for children, clear guidance should be developed to allow consistency in practice across the healthcare professionals who are involved with such medicines in their routine practice.

Introduction:

Even though, it is well documented that children are not small adults,[1,2] many of the medicines currently used to treat children are based upon extrapolation of adult data.[3,4] This is due to the fact that many medicines are only tested in and licensed for adult patients.[5] A review of 30 studies carried out between 1984 and 2004, showed that 11-37% of drugs prescribed to children in the community setting, 16-62% prescribed in general paediatric wards and up to 80% in neonatal intensive care units are either unlicensed or used in an off-label manner (i.e. prescribed outside their product license with respect to age, dose, route of administration or indication).[6] Despite this wide-spread use of unlicensed/off-label medicines in children, only 40% of General Practitioners (GPs) admit to unlicensed/off-label prescribing.[7] In addition, a study has shown that in a cohort of 95 French paediatricians, 92% of the paediatricians did not recognise the off-label status of the medicines they prescribed.[8] Another study conducted recently in 4 Italian paediatric hospitals, found a discordance between the existing prescribing and physicians' perceptions of off-label prescribing. This was explained by the fact that paediatricians did not consider some of the most commonly prescribed drugs in their everyday practice as being off-label.[9] Off-label/unlicensed prescribing for children is a global problem, however, recent major research initiatives in the USA and Europe are beginning to address the issue of the need for a greater evidence base for the safe and effective use of medicines in this age group.[10]

In the meantime, off-label/unlicensed prescribing often represents the most rational use of medicines if no approved alternatives for children with comparable benefit-risk ratio are available.[10] Very often some data are available on paediatric use, which ranges from scarce

to adequate for market authorisation, but even when adequate data are available, these have not been submitted by a pharmaceutical company to the regulatory authorities for evaluation and no age appropriate formulations are available. [10]

There is growing concern about the safety and efficacy of unlicensed/off-label medicine use in children particularly due to the lack of long-term safety and efficacy data in this vulnerable group and due to evidence suggesting an increased risk of adverse drug reactions (ADRs) and treatment failure.[11-13] The ethical obligation of providing the best available treatment to children coupled with a lack of availability of licensed paediatric products, highlights the need for an increased number of clinical trials in children. Performing such trials, however, requires special attention to the various challenges faced in this population.[14]

To date, limited data have been published on the views and experiences of different healthcare professionals on these matters. The aim of the present study was, therefore, to investigate the knowledge and views of a wide range of healthcare professionals (including consultant paediatricians, GPs, community pharmacists and paediatric nurses) regarding the use of unlicensed/off-label medicines in children and the participation of children in clinical trials.

Methods:

A survey instrument comprising 39 questions (Appendix 1) was designed after extensive literature review. The questionnaire focused primarily on the use of unlicensed and off-label

medicines in children and consisted of five sections addressing different topics of interest together with a separate section concerning participant details and demographics (to allow examination of variability in responses according to participant characteristics): The first section focused on the experiences and views of healthcare professionals regarding the use of unlicensed and off-label medicines in children while the second section focused on parental involvement in decision making regarding the medicine being prescribed for their child. The third section addressed the information sources that healthcare professionals use when prescribing, dispensing and administering unlicensed/off-label medicines to children. The fourth section focused on paediatric clinical trials while the final section focused on dose-related issues when prescribing unlicensed and off-label medicines in children. Information (definitions and examples) regarding the unlicensed/off-label use of medicines in children was provided as an integral part of the questionnaire to guide respondents who were not familiar with the terminology.

Prior to the full study, the questionnaire was piloted in a small number of healthcare professionals (n=20) (Pharmacists and Doctors); these results were not included in the final analysis. The respondents indicated that the questionnaire was clear and easy to understand. The questionnaire was then posted to GPs, community pharmacists and hospital based paediatric nurses and e-mailed to consultant paediatricians across Northern Ireland. The questionnaires were mailed to 500 randomly selected GPs (http://allen.netcom.co.uk/Sampling.htm) and all community pharmacists (n=512). The recipients were allowed four weeks to return the completed questionnaire. A letter was also sent to paediatric nursing units of all hospitals in Northern Ireland. The letters were sent to the head of each ward asking them to reply if they were willing to have their nursing staff

take part in this study and if this was the case, they were also asked to indicate the number of questionnaires that would be required in each unit. Questionnaires (n=150) were sent to these units which agreed to take part in the study giving them a four week period to complete the questionnaire.

Finally, questionnaires were e-mailed to all consultant paediatricians in Northern Ireland (n=50) giving them four weeks to complete the questionnaire. This survey was not sent to hospital pharmacists due to the small number of specialist paediatric pharmacists in Northern Ireland. Following data collection, responses were coded and entered into a customised database in SPSS, version 15, for statistical analyses (Chi-square test and sign tests). Consultation with the Office of Research Ethics Committees in Northern Ireland (ORECNI) confirmed that the study did not require formal review by the National Health Service (NHS) ethics committee. The study, however, received ethical approval from the School of Pharmacy, Queen's University Belfast Research Ethics Committee.

Results:

Demographics

Out of the 1,212 distributed questionnaires, 563 (46.5%) were returned completed and 32 uncompleted. A total of 59.8% of GPs, 32.8% of community pharmacists, 72.0% of consultant paediatricians and 43.3% of paediatric nurses replied. The majority of respondents were female (59.2%) and aged between 20-40 years old (60.8%).

Knowledge and views about unlicensed/off-label medicines

The majority of respondents (467; 82.9%) indicated that they were familiar with the term, unlicensed medicines while 330 (58.6%) indicated they were familiar with the term off-label medicines prior to receiving the questionnaire. There was a significant difference in the familiarity with unlicensed/off-label prescribing among the different sectors of health care professionals ($P<0.05$) with community pharmacists being most familiar with the term unlicensed medicines (93%) and consultant paediatricians most familiar with the term, off-label medicines (83.3%). When asked how they became familiar with the terminology of unlicensed and off-label medicines, 51.7% of respondents said they had gained their knowledge through their professional experience rather than through undergraduate (24%) or postgraduate (16.5%) training. Separate analysis for community pharmacists, however, indicated that they had gained their knowledge mainly through their undergraduate studies (50.0%) rather than through their experience (39.0%) or postgraduate studies (33.1%), the latter data being significantly different ($P<0.05$) from corresponding results for other groups.

Approximately one quarter (24.5%) and one third (31%) of the respondents reported actually prescribing, dispensing or administering unlicensed and off-label medicines, respectively, to children in their practice during the four weeks that preceded answering the questionnaire. They reported that the reasons for off-label prescribing were younger age (33.6%), lower than recommended dose (30.7%), higher than recommended dose (29.1%), different indication (29.1%) or different route of administration (24.2%) from that of the licensed product. No significant differences in the perceived reasons for off-label prescribing were found among the different healthcare professionals ($P>0.05$). In addition, the majority

of respondents reported infants (1 to 23 months of age) to be most likely to receive unlicensed (40.9%) or off-label (35.0%) medicines. On the other hand, children from 2 to 11 years old and children from 12 to 18 years old were, according to the respondents, less likely to receive unlicensed (22.1%) or off-label (33.0%) medicines (Table 1).

When asked to rank the most important ways by which unlicensed and off-label medicine use in children could be reduced, the majority of respondents (60%) ranked making more appropriate formulations available for younger children as a 'very important' approach, followed by increasing clinical trials for new drugs (38.5%) and finally increasing clinical trials for existing drugs (28.6%). There were no significant differences between different groups of health care professionals with regards to this subject ($P>0.05$).

Views about the safety and efficacy of unlicensed/off-label medicines

The majority of respondents had major and/or minor concerns regarding the safety (77.8%) and the efficacy (87.9%) of unlicensed and off-label medicine use in children. Safety and efficacy concerns were more frequently raised by pharmacists and GPs when compared with consultant paediatricians and paediatric nurses (89.0%, 93% vs 83.3%, 64.4% for safety and 81.7%, 80.3% vs 69.4%, 61.5% for efficacy; $P<0.05$; Chi Square test). Concerns about the safety of unlicensed and off-label medicines in children were addressed again in a further question which examined whether respondents felt that the use of unlicensed and off-label medicines increased the likelihood of ADRs when compared with licensed medicines in children. Results for each group of respondents are presented in Figure 1. Discussing their own practice, approximately one quarter (23.8%) of respondents admitted to having

experienced treatment failure while 11.2% to having observed ADRs when prescribing, dispensing or administering unlicensed/off-label medicines in children. Interestingly, there was a significant relationship between those participants who reported experiencing treatment failures (23.8%) and those who reported lower than recommended doses as the main reason for off-label use (30.7%; $P<0.01$). In addition, there was a significant correlation between those who reported experiencing cases of ADRs (11.2%) and those who reported higher than recommended dosing as being the main reason for off-label use (29.1%; $P<0.05$). Treatment failures and adverse effects were reported by more consultant paediatricians when compared to the other respondent groups (i.e. 41.7%, 28.9%, 15.9%, 10.7% for treatment failure vs 25.0%, 11.7%, 8.5%, 7.6 for ADRs; same categories as Figure 1).

When asked about which is more problematic with regard to safety, approximately one quarter of respondents (26.8%) thought that the use of unlicensed medicines was more problematic when compared to off-label medicines. However, almost half the respondents (48.5%) felt that the use of unlicensed and off-label medicines is equally problematic with regard to safety.

Dosing-related issues and information sources

The vast majority (93.4%) of respondents said they double checked doses of medicines used in children if a calculation was required in deciding on the dose. Interestingly, 78.3% of respondents had come across a dosing error in a paediatric prescription in their professional practice. Almost half of respondents (43.7%) felt that licensing more medicines for use in

children would decrease dosing errors in children. However, GPs and community pharmacists had stronger views than consultants and paediatric nurses in this regard (47.0% and 55.5% vs 8.3% and 18.5%, respectively). When asked about the various information sources they used when dealing with medicines in children, respondents reported that the British National Formulary for Children (BNFc) was the most commonly used, followed by the British National Formulary (BNF), Table 2. In addition, they stated that, of all sources, the BNFc contained the most appropriate information to support their practice.

Communication with parents and guardians

Although 85.4% of respondents agreed that parents/guardians should be told when an unlicensed or off-label medicine was prescribed for their children, only 30.7% of respondents reported informing parents and guardians when such medicines were used. Only 1.1% of respondents said that they request written consent from parents or guardians, while 45.1% said that they request verbal consent when informing parents about the unlicensed/off-label use of medicines. GPs were the group that most frequently claimed informing parents (41.9%) and asking for verbal consent (39.3%).

Overall, respondents felt that parents should be informed by the doctor (95.7%), pharmacist (2.3%) or nurse (0.5%) within the hospital setting while in primary care, the providers of the information were selected as follows: the doctor (94.0%) and the community pharmacist (4.6%).

Clinical trials in children

When asked about the need for more paediatric clinical trials to address the issue of unlicensed/off-label medicine use, 56% of the respondents believed that medicines used in an unlicensed/off-label fashion should undergo clinical trials in children. This percentage was reasonably consistent for all healthcare professional groups (i.e. 55.6%, 52.7%, 64.9%, 49.3%; same categories as Figure 1). Moreover, approximately half of respondents (54.7%) agreed that pharmaceutical companies should be forced to carry out research on new medicines in children. However, only 28.4% of respondents indicated that they would be willing to be actively involved in, and recruit their own patients for, paediatric clinical research. Consultant paediatricians (94.4%) reported most willingness to help with clinical trials when compared with other health care professional groups (Figure 2).

Respondents were also asked if they would consent for their own children to participate in clinical trials. No significant difference was found between those who had children of their own and those who did not ($P>0.05$; Chi Square test). However, this willingness was influenced by the assumed health status of the child and whether the medicine was new or an existing medicine used in unlicensed/off-label manner (Figure 3).

Discussion:

The lack of alternate approved medicines for children, and the lack of paediatric formulations even if data on paediatric pharmacology of a drug are available, mean that off-label and unlicensed prescribing continues to be a necessary feature of contemporary paediatric practice. To our knowledge, this is the first study to contemporaneously assess the levels of knowledge and views on unlicensed/off-label medicines in children in a range of healthcare professionals (consultant paediatricians, GPs, community pharmacists and

paediatric nurses); 1,212 healthcare professionals throughout Northern Ireland were approached in this survey, with approximately half of them responding.

The majority of consultants, GPs and community pharmacists were familiar with the concept of unlicensed/off-label prescribing. The most commonly reported reason for such prescribing was 'use at a younger age than recommended'. This finding was consistent with earlier studies examining views/attitudes of GPs and community pharmacists in the UK [7,15] and matches actual data collected in a survey of UK hospital-based prescribing. [16] In the community setting in the UK,[17] however, 'lower dose than recommended' has been shown to be the most frequent cause for off-label prescribing while younger age than recommended is amongst the least frequent reason for this mode of medicine use.

Apart from the pharmacists, most respondents (including GPs) reported having gained their knowledge through personal experience rather than via their undergraduate or postgraduate training, a similar situation to that reported in an earlier study.[7] This reliance on personal experience highlights a significant deficiency in current healthcare undergraduate and postgraduate education.

It was interesting to note that a very low percentage of healthcare professionals inform parents or seek their consent when an unlicensed or off-label medicine is prescribed, dispensed or administered to a child. This finding coincides with a recent study performed in Germany that showed a limited and surprisingly low knowledge of off-label prescribing among parents of chronically ill children.[18] In an earlier public opinion survey carried out in Northern Ireland, a significant percentage of parents/guardians reported that they would

refuse the use of such medicines or ask for the prescription of a licensed alternative if they were informed about the unlicensed use of medicines in their child. In addition, the majority of participants in that latter study (92.1%) felt that parents should be told if their child was being prescribed a medicine that had not been fully studied or licensed in children.[19]

A large number of respondents expressed concerns regarding the safety and efficacy of unlicensed/off-label medicines and reported cases of treatment failure and side effects of such agents during their practice. Paediatric nurses were the least concerned about safety/efficacy issues when compared with the other groups of healthcare professionals. This could be attributed to them being very accustomed to treating large numbers of children, many of whom will receive medicines outside the licensed recommendations. Another interesting result was the fact that the reported experiences of treatment failure in this study were higher than experiences of ADRs following the use of unlicensed/off-label medicines in children. This may reflect clinicians being over cautious in using appropriately high doses. This was supported by the fact that experiences of treatment failures were associated with 'lower than recommended' dosing being identified as the main reason for off-label use.

The vast majority of respondents (93.4%) claimed that they double checked the doses of medicines used in children when a dosage calculation is required. In doing this, more than three quarters of respondents reported that they had come across a dosing error in a paediatric prescription in their professional practice. Concern about this high incidence of error detection is compounded by the fact that the literature shows that medication errors

in children receiving unlicensed/off-label medicines have three times the potential to cause harm when compared with similar errors in adults.[20]

Surprisingly, only half of the respondents believed that unlicensed/off-label medicines should undergo clinical trials in children despite their concerns about their safety and efficacy. These findings were consistent with a recent survey of the attitudes of hospital based paediatricians [21] in Scotland but in contrast with those expressed by Scottish GPs who were more convinced of the need for appropriate clinical trials in children.[7] In order to conduct such clinical trials there needs to be an increased willingness of both clinicians and parents to become involved in this type of research. Such willingness was found in the present study to be very much higher in consultant paediatricians when compared with the other professional groups (Figure 2). It has been shown that the willingness of parents to consent for their children to take part in clinical trials is associated with the worsening of the child's health status and when children can directly benefit from the clinical research.[18,19] The present study showed that this also holds true for healthcare professionals who are themselves parents.

Overall the research indicated that still much remains to be achieved in the area of both managing off-label and unlicensed medicine use and in creating the environment in which research in children to improve the evidence base is integrated into routine practice.

Conflict of Interests:

The authors declare that they have no conflict of interest.

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Table 1: Unlicensed and off-label medicine prescribing, dispensing and administration to children by the different health care professionals **

	Consultant paediatrician		General practitioner		Community pharmacist		Paediatric nurse	
	U.L.*	***O.L.****	***U.L.****	***O.L.****	***U.L.****	***O.L.****	***U.L.****	***O.L.****
Neonates, including preterm and full term babies from birth to 28 days	52.8%	41.6%	36.9%	33.2%	36.6%	30.5%	23.1%	24.6%
Infants from one to 23 months	36.1%	34.2%	38.6%	33.5%	47.6%	37.8%	44.6%	33.9%
Children from two to 11 years	11.1%	19.4%	17.8%	24.2%	13.4%	34.7%	24.6%	36.9%
Children from 12 to 18 years	0.0%	2.8%	6.7%	9.1%	2.4%	0.0%	7.7%	4.6%

** U.L.: unlicensed medicine, O.L.: off-label medicine*
***The data refer to activities in the last four weeks*
There was no statistically significant difference between the rates of use between the different professionals group (P> 0.05)

Table 2: Information sources used by healthcare professionals when prescribing, dispensing or administering unlicensed and off-label medicines to children

	Very frequently	Frequently	Rarely	Never	Contains sufficient information
New BNFc	252 (44.8%)	230 (40.9%)	79 (14.0%)	2 (0.4%)	*91.8%*
BNF	151 (26.8%)	268 (47.6%)	99 (17.6%)	45 (8.0%)	*72.8%*
Medicines for Children	83 (14.7%)	66 (11.7%)	113 (20.1%)	301 (53.5%)	*30.9%*
Monthly index of medical specialties	40 (7.1%)	114 (25.6%)	147 (26.1%)	231 (41.0%)	*24.3%*
Summary of product characteristics	10 (1.8%)	57 (10.1%)	232 (41.2%)	264 (46.9%)	*21.7%*
Local formulary	9 (1.6%)	42 (7.5%)	156 (27.7)	356 (63.2%)	*11.5%*
National guidelines	13 (2.3%)	95 (16.9%)	214 (38.0%)	241 (42.0%)	*18.1%*

(P>0.05 in all cases when different professionals groups compared; Chi Square test)

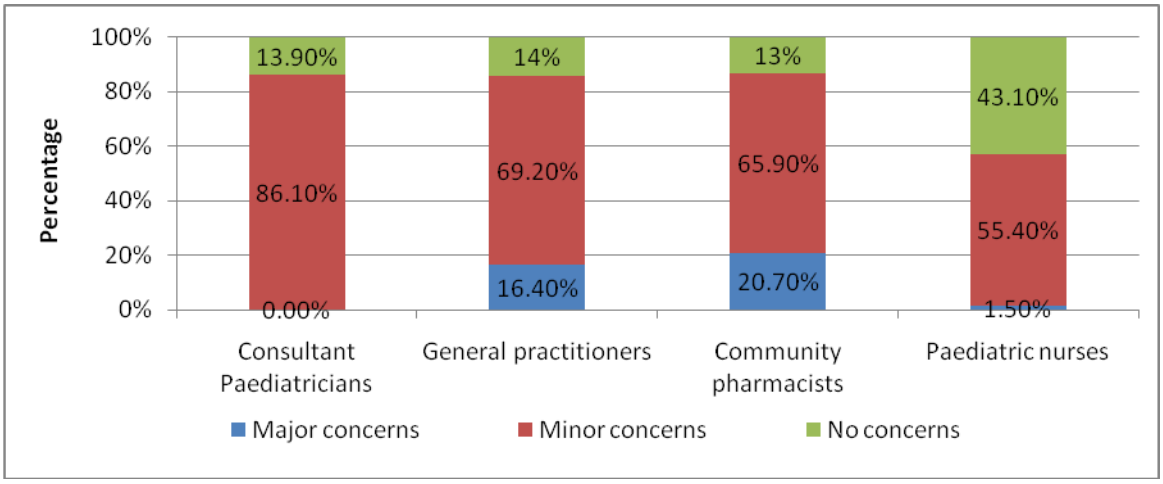


Figure 1: Respondents' concerns regarding the likelihood of unlicensed and off-label medicines increasing the level of adverse drug reactions in children (P<0.05; Chi Square test)

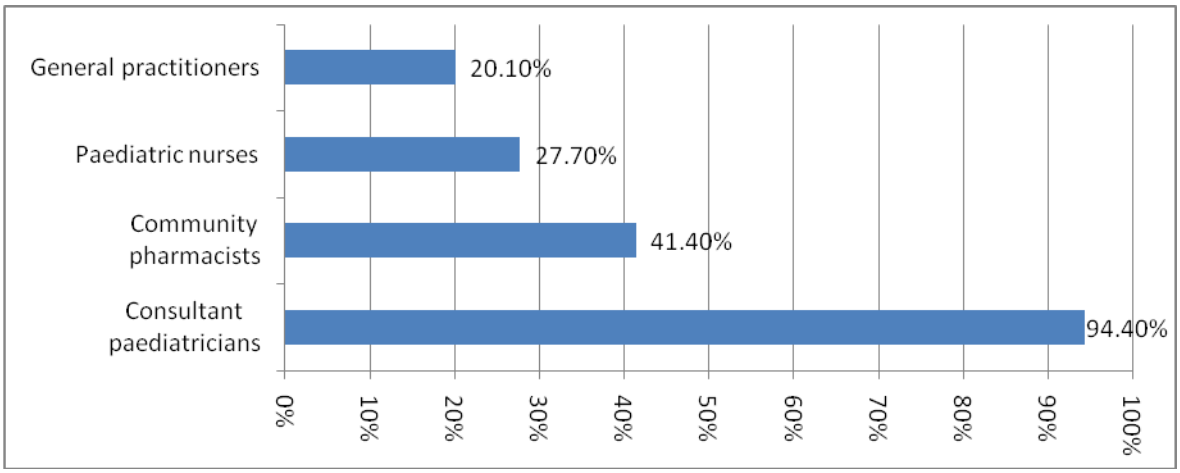
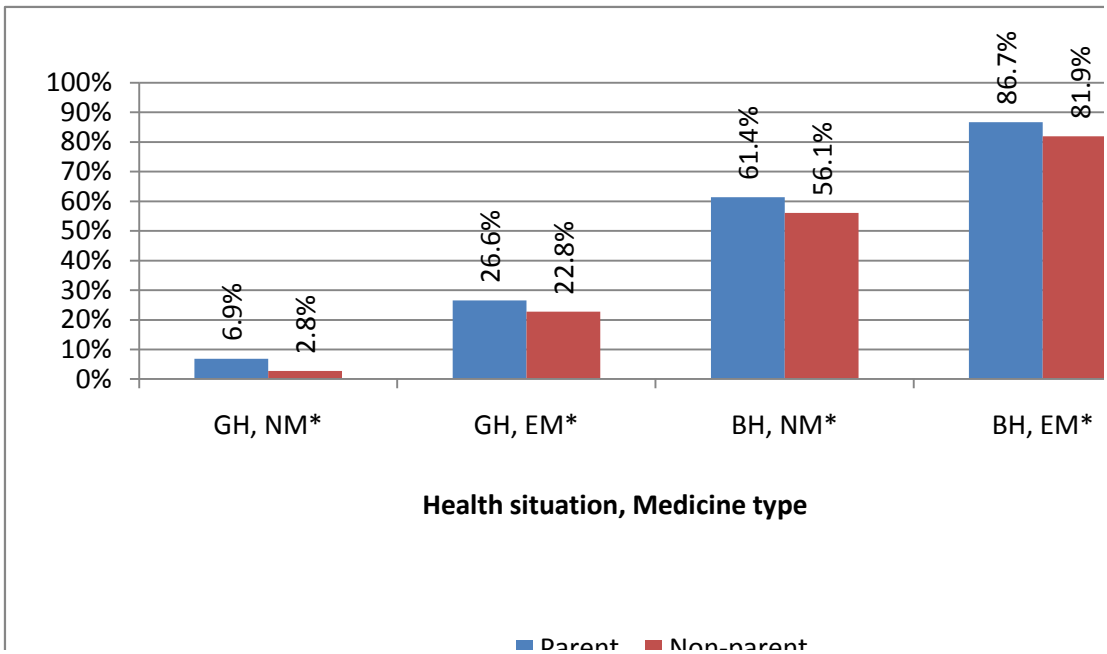


Figure 2: Willingness of different healthcare professional groups to be actively involved in paediatric clinical trials, i.e. help in recruiting patients.



GH – child in good health
BH – child has condition for which the medicine could be beneficial
NM –new medicine which has not received a license for adult use
EM – medicine which is licensed for adult use.

Figure 3: Respondents (parents vs. non-parents) responses regarding enrolling their child in a clinical trial based on their child's health status and whether the medicine to be tested was a new medicine or an existing medicine used in an unlicensed or off-label manner.

APPENDIX 1. THE USE OF UNLICENSED AND OFF-LABEL MEDICINES IN CHILDREN

Definition: The International Conference on Harmonisation (ICH) has defined children to be individuals of both sexes who range between 0 and 18 years of age. This age range has been used in this questionnaire.

For each question please circle the option which you agree with, unless the question tells you to choose more than one option.

I. Experiences and views regarding medicines for children

1. In your opinion, how safe are medicines that are prescribed for use in children?
(a) Extremely safe (b) Safe (c) Unsafe (d) Extremely unsafe (e) I don't know

Prior to drugs being marketed they undergo trials to ensure safety and efficacy in adult volunteers and patients. If the results are positive, and meet strict criteria, a license is granted to market the medicine. Treatment of children may involve use of medicines without a license (unlicensed). Unlicensed medicines include those which: are prepared from basic ingredients within the pharmacy; are modifications of a licensed medicinal product, for example, an oral liquid preparation made from crushed tablets.

Medicines can also be prescribed for children off-label. Off-label means that the medicine is licensed, however, it is being used outside the license recommendations with respect to the dose, indication, route of administration or recommended age, for example, increased number of puffs of an inhaler in an attempt to improve efficacy; use of intramuscular vitamin K injection by the oral route. Such use of medications is, however, necessary in paediatric practice to offer the best treatment for sick children.

2. Before completing this questionnaire, were you familiar with the definition for *unlicensed medicines*?
(a) Yes (b) No

3. Before completing on this questionnaire, were you familiar with the definition for *off-label medicines*?
(a) Yes (b) No

4. When did you first hear about the use of unlicensed or off-label medicines?
(a) in my undergraduate studies
(b) in my post graduate studies
(c) through my experience in my work
(d) the terminology was new to me

5. During the *last 4 weeks*, how many times did you prescribe/dispense/administer an *unlicensed medicine* to a child in your practice.
_____ times (please insert number; if none insert 0)

6. During the *last 4 weeks*, how many times did you prescribe/ dispense/ administer an *off-label medicine* to a child in your practice.

_____ times (please insert number; if none insert 0)

7. Regardless of your own practice area, which of the following age groups of children in general do you feel are most likely to receive unlicensed medicines? (please tick one box only)

Age Group	
Neonates, including preterm and term from birth to 28 days	
Infants from 1 to 23 months of age	
Children from 2 to 11 years of age	
Children from 12 to 18 years of age.	

8. Regardless of your own practice area, which of the following age groups of children in general do you feel are most likely to receive off-label prescriptions? (please tick one box only)

Age Group	
Neonates, including preterm and term from birth to 28 days	
Infants from 1 to 23 months of age	
Children from 2 to 11 years of age	
Children from 12 to 16 years of age.	

9. Please indicate which of the following you feel is the most common and which is the least common reason for off-label prescribing. Please score 1-5 with 5 the most common and 1 the least common.

Lower than recommended dose used e.g. Extended dosage interval to take account of possible decreased elimination in children.	
Higher than recommended dose used e.g. the use of a higher dose in an attempt to improve effectiveness.	
Use at a younger age than recommended e.g. the use of medicines in infants when the medicines are only licensed for use in older children.	
Use of medicine via a different route of administration e.g. Oral administration of intramuscular preparations due to non-availability of an oral liquid formulation.	
Use of medicine for a different indication (from the licensed indication) e.g. the use of anti-inflammatory medicines to treat pain in children.	

10. In general, do you have concerns about the *efficacy* of *unlicensed and off-label medicine* use in children?

(a) Yes, a lot more concerns than for licensed medicines

(b) Yes, some more concerns than for licensed medicines

(c) No, no more concerns than for licensed medicines

11. In general, do you have concerns about the *safety* of *unlicensed and off-label medicine* use in children?

(a) Yes, a lot more concerns than for licensed medicines
(b) Yes, some more concerns than for licensed medicines
(c) No, no more concerns than for licensed medicines

12. In general do you feel that the use of *unlicensed and off-label medicines* increases the likelihood of adverse drug reactions (side effects) when compared with licensed medicine use in children?

(a) Yes, a major increase in the likelihood of adverse drug reactions
(b) Yes, some increase in the likelihood of adverse drug reactions
(c) No, no increase in the likelihood of adverse drug reactions

13. Have any children that you have previously dealt with, to your knowledge, ever experienced an adverse drug reaction following the use of *unlicensed or off-label medicines*?

(a) Yes (b) No
(c) Do not come across unlicensed and off-label medicines for children in my practice

14. Have any children that you have previously dealt with, to your knowledge, ever experienced treatment failure following the use of *unlicensed or off-label medicines*?

(a) Yes (b) No
(c) Do not come across unlicensed and off-label medicines for children in my practice

15. In your opinion which of the following is the *most* problematic with regards to *safety*? (Please circle one answer only)

(a) the use of **unlicensed** medicine in children
(b) the use of **off-label** medicines in children
(c) The use of **unlicensed and off-label** medicines is equally problematic.
(d) I don't consider the use of **unlicensed or off-label medicines** in children to be a safety issue.

16. Please rank the following according to their importance in reducing the use of u*nlicensed and off-labeled medications* in children? (Please tick one box per statement).

	Very important	Important	Unimportant	Very unimportant
Increase the number of clinical trials for new drugs in children				
Increase clinical trials for existing drugs in children				
Make more appropriate formulations available for young children				

II. Parent and guardian involvement

17. In your view, should parents or guardians should be routinely told when an unlicensed or off-label medicine is prescribed/dispensed/ given to their child.

(a) Yes (b) No

18. Do you inform parents or guardians when an *unlicensed or off-label medicine* for their child has been prescribed/ dispensed/ administered?

(a) All of the time (b) Some of the time

(c) Never (d) Do not come across unlicensed and off-label medicines for children in my practice.

19. Do you request informed, *written consent* from parents or guardians before prescribing/ dispensing/ administering *unlicensed or off-label medicines* to their child?

(a) Yes (b) No

(c) Do not come across unlicensed and off-label medicines for children in my practice

20. Do you request informed, *verbal consent* from parents or guardians before prescribing/ dispensing/ administering *unlicensed or off-label medicines* to their child?

(a) Yes (b) No

(c) Do not come across unlicensed and off-label medicines for children in my practice

21. Who do you think has the main responsibility to inform parents or guardians that their child is being treated using an *unlicensed or off-label medicine in the hospital setting*?

(a) The doctor (b) The nurse

(c) The pharmacist (d) Parent or guardian does not need to be informed

22. Who do you think has the main responsibility to inform parents or guardians that their child is being treated using an *unlicensed or off-label medicine in primary care?*

(a) The doctor (b) The pharmacist

(c) Parent or guardian does not need to be informed

23. I think that it would unnecessarily worry parents or guardians if I told them that a medicine that their child was being treated with was being used in an *unlicensed or off-label manner.*

(a) Strongly agree

(b) Agree

(c) Disagree

(d) Strongly disagree

III. Information sources

24. When prescribing/dispensing/administering medicines for children, to what extent do you use the following information sources:

(Please also indicate whether you feel each source contains sufficient information for you needs)

	Very frequently	Frequently	Rarely	Never	Contains sufficient information for my needs: (Yes / No)
New BNFc (British National Formulary for children's medicines)					
BNF (British National Formulary)					
Medicines for Children					
MMS (Monthly index of medical specialties)					
Summary of product characteristics					
Local formulary					
National guidelines					

IV. Testing medicines for use in children

25. Should all existing medicines that are commonly used in an unlicensed or off-label manner in children undergo clinical testing in children suffering from the indication(s) in question, so that they can be licensed for the use in children?
(a) Yes (b) No (c) Don't know

26. Should manufacturers be forced to test all new medicines (with a potential for paediatric use) in children suffering from the indication(s) in question, as part of the drug development process?
(a) Yes (b) No (c) Don't know

27. Would you be willing to be actively involved in conducting clinical trials in children e.g. help in recruiting patients?
(a) Yes (b) No

28. Before participating in a clinical trial, children's parents or guardians should approve that their child can take part in a clinical trial by signing a consent form. At what age do you feel children are old enough to understand the implication of taking part in clinical trials and as such give their verbal assent to participate in clinical trials?
_____-
_____

29. In your opinion, what are the main barriers that prevent more widespread testing and licensing of medicines for use in children?
_____
_____

30. Do you think that children in general should participate in clinical trials? Please consider the following scenarios.

	If s/he is in good health		If s/he is suffering from a condition for which the medicine could be beneficial	
For studying and testing a new drug (which although tested in man has not yet received a license for adult use)	**Yes**	**No**	**Yes**	**No**
For studying and testing an existing drug (i.e. one which is already licensed for adult use)	**Yes**	**No**	**Yes**	**No**

31. Would you allow your own child to participate in clinical trials? (If you do not have a child, for the sake of this question please assume that you have a child) Please consider the following scenarios.

	If s/he is in good health		If s/he is suffering from a condition for which the medicine could be beneficial	
For studying and testing a new drug (which although tested in man has not yet received a license for adults use)	**Yes**	**No**	**Yes**	**No**
For studying and testing an existing drug (i.e. one which is already licensed for adult use)	**Yes**	**No**	**Yes**	**No**

Please complete the following:

☐ I have a child/ children Ages _____ _____ _____ years

☐ I do not have a child of my own

V. Dosing Issues

Medicine use in children may require extrapolating the dose based on the weight or surface area of the child, from the dose used in adults.

32. Do you routinely double check doses of medicines used in children if a calculation was required in deciding on the dose to be given?

(a) Yes (b) No

33. Have you ever come across a dosing error in a paediatric prescription?

(a) Yes (b) No

34. Do you think that licensing more medicines for use in children will decrease dosing errors in paediatrics?

(a) Yes (b) No (c) Don't know

VI. General information about yourself

35. Age group:

21-30	
31-40	
41-50	
51-60	
Over 60	

36. Sex

(a) Male (b) Female

37. You are a:

(a) Consultant paediatrician (b) A&E consultant (c) GP

(d) Community pharmacist (e) Hospital pharmacist (f) Nurse

38. How long have you been a qualified healthcare professional?

_____ Years

39. Approximately what proportion of your practice comprises children? _____ %

THANK YOU VERY MUCH INDEED FOR ASSISTING WITH THIS RESEARCH