The MSL: Earned every stripe and adding to them to future proof our path
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Acknowledgement:
The MSLA would like to acknowledge the kind article contributions from Dr Rina Newton of CompliMed and Andrea Litovszky & Jon Elliott AXESS Ltd.

Front Cover competition:
Each MSLAJ edition will carry a new front cover and you are invited to submit original artwork / photography that you feel would suit, reflect, empathise with the role of the working MSL. The editorial board will select the winner who will not only have their artwork grace the front cover, but also one free access to an MSLA event within 12 months of the issue publication date. Please submit entries to journalmsla@gmail.com along with your name, email & contact number.

Front Cover this issue:
Artwork & Design: Zaynah Saleheen
Formatting & digitisation: Adam Malik
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Foreword:

Dear Colleagues

Welcome to the third and final 2018 issue of the Journal of The Medical Science Liaison Association (UK & Ireland) - MSLAJ.

This is a new and exciting resource for the UK & Ireland MSL Community to create a cross-company common platform to share and drive best practice and ultimately enhance the compliance, value, credibility and sustainability of the MSL role.

So as you enjoy some well deserved time away from work, as you eat more than you probably should and watch The Snowman (other Christmas films exist!) What better festive accompaniment is there than the third issue of the MSLAJ?

Huge thanks to all the article contributors, without you the MSLAJ is nothing. An important thank you to Zaynah Saleheen: the MSLAJ front cover winner for this issue.

Finally, thanks to Zulfi Malik, who has spearheaded the MSLAJ from its inception. He will be asking for MSLA membership support to continue producing such a high quality journal as we move into 2019. Look out for more info and please continue to email your questions, enquiries, article suggestions / submissions or comments to: journalmsla@gmail.com

The date you’ve been waiting for is now able to be publicised: MSLA 2019 annual conference will be held on Wednesday 27th March at the Hilton Birmingham Metropole (again). Of course the conference wouldn't be the same without our annual Networking Evening - Tuesday 27th March.

SAVE THESE DATES! Registration will open in early January - we will email all members when it is accessible.

Happy reading and happy holidays. Thank you for your great ongoing support of the MSLA.

Roger Berry (MSLA chairman)
Zulfi Malik (MSLA Treasurer and MSLAJ Project Lead)
MSLA Journal Cover Competition!

Thank you to all those who made the effort to submit a photo, piece of artwork - digital and otherwise for the Journal's Front Cover competition!

The Editorial team is proud to announce that the winner for this issue is:

Zaynah Saleheen, MSc

Zaynah is an aspiring MSL and became a member of The MSLA to gain further insights into the role and network with current MSLs. She is an experienced Senior Research Executive with a demonstrated history of working in the pharmaceuticals industry. Skilled in Customer Insight, Life Sciences, Data Analysis, Quantitative Research, and Research Design. Strong marketing professional with an MSc focused in neuro-imaging from King's College London, Institute of Psychiatry.

Very well done Zaynah! You win a FREE entry to an MSLA event of your choice within the next 12 months, be it one of our acclaimed 'How to...' educational seminars or indeed the next annual conference.

The MSLA Journal Cover Competition is once again open for Mar-Apr (MSLAJ Vol. 2 Issue 1, 2019)

Please submit your Front-Cover artwork any time between now and 15 March, 2019 All journal communications, including competition entry to: journalmsla@gmail.com
The Healthcare Operating Landscape and the MSL: Evolving together

Christine Mackay MBA, CMgr MCMI
MSLA Executive Committee Member

Introduction

The global pharmaceutical industry is in a period of change. Healthcare markets across the world are evolving to meet the needs of their populations, and are subject to internal pressures to provide safe and effective treatments at affordable prices. Demand is increasing in emerging markets whilst markets are static or declining in developed countries. At the same time, the regulatory agencies are demanding more evidence from companies before approval to launch a new drug is granted.

The industry is also facing questions beyond products and processes, such as culture, new customer and consumer engagement, talent management, and how to successfully spot future trends and profitable areas for diversification or development. Combined with the revolution in technology and data, these, and other factors, create a need for companies to assess their business strategies, and to identify, cultivate, and exploit their competencies in order to compete successfully in the evolving environment.

For MSLs, it is important for us to understand the strategic choices our organisations and potential future organisations are making, and to build our own knowledge and competencies, and adapt our role, within the regulatory and ABPI frameworks, to fit these different and evolving models of business.

The market and the MSL

The ethical pharmaceutical market is made up of three broad types of organisations; ‘Big Pharma’ who have an emphasis on developing new molecules and bringing innovative medicines to market, generics companies focused on patent-busting and mass market cost leadership, and specialist or niche companies. There are strong interdependencies and overlap of these groupings and this is where the role of the MSL is most widely established.

A more recent development is the entry of companies such as Samsung, in partnership with existing industry players, who see drugs as a potential area of growth, especially the expensive biologics classes. If they are able to compete on manufacturing and marketing the complex biologics, and utilise competencies of their experienced new partners, then they may take a large slice of the market without investment in R&D, becoming a generic biologics or biosimilars company. MSL roles are established in the current partner organisations, and it will be interesting to observe any influence of the non-pharma players’ culture on the expectations and activities of these MSLs. There may be innovation transfer that the traditionally conservative pharma industry can implement or adapt to the advantage of the role.

There are also a number of other industry players, for example R&D companies that form alliances to commercialise their discoveries, and companies with competencies in distribution or supply might acquire others with promising late stage products. There are also consumer healthcare companies that have products in the prescription market, such as Reckitt Benckiser, and there are
products that are in both markets, such as vitamins and aspirin. Few of these organisational models have MSL support as part of UK operations currently, so are not the focus of this paper.

Organisational strategy choices

Though the majority of MSLs are employed by either larger ‘big pharma’ or smaller ‘niche’ ethical, research-based healthcare companies, these are not a homogeneous category. The choice of operating model, which customers to engage with and how, which disease areas to prioritise, and what competencies to develop, will have a significant influence on how many MSLs they employ, and what activities the MSLs carry out.

Some of the strategic options available to healthcare companies are outlined below:

• Innovative R&D driven company, rooted in the current Big Pharma model. Use energy on inventing, developing and bringing new drugs to market despite the increasing cost and risk of failure.

• ‘Me-too’ company, with core competencies in rapid commercialisation and marketing of third or fourth in class treatments, or innovating existing molecules discarded by the larger companies. Focus on customer engagement, marketing and cost value.

• Chronic disease management companies, to interact more with individual patients and patient groups and provide a range of drug and complementary disease management therapies, ie. Biologics, NSAIDS, dieticians and physiotherapy for rheumatoid arthritis.

• Generics Company with core competencies in logistics and process efficiency. Driven by economies of scale, price will be key and choice and quality will be adequate.

• Lifestyle choice company, to include prevention, minor ailments not covered by insurance, some obesity products, vitamins etc. Roots in consumer healthcare but expanding to meet wider needs as insurance coverage reduces.

• Private health provision, offering personalised and concierge services, gene therapy, health screening and prevention. Available to niche wealthy consumers.

It is possible for one company to operate more than one business model based on the stage of their product lifecycles, so by adopting one of these strategies it does not preclude operating in all others. There are some models which are exclusive, ie generics and R&D innovators, but there are others where overlap is possible, ie. R&D focused and chronic disease management companies. Providing they have a complete understanding of operating strategy and what is needed from a medical team, MSLs can define a role in any of these models, with external stakeholder engagement at the core.

Generally, the larger the organisation and its internal resources, the smaller the range of activities the MSLs undertake. In smaller organisations that may have one or two MSLs, the opportunity for MSL in-role development and job satisfaction is potentially much higher, given the level of personal responsibility and involvement in strategically important and diverse activities. This will naturally be based on individual MSLs’ motivation and preferences. In a larger organisation it may be that MSLs are at the bottom of a departmental hierarchy, an implementer of tactics rather than a strategic and valued partner, and this has implications for MSL talent management and retention.
MSL future proofing

The MSL roles being carried out in the environment and organisations discussed above are unlikely to be the same in 5, 10 or 20 years from now, given the rapid patient, policy, economic, technology and therapy area changes underway in the healthcare landscape. To ensure MSLs remain relevant going forward we might consider where and how MSLs can ‘become’ a core competency of our organisations, and what the gaps are that we need to fill to ensure the continuance of our role.

This ‘gap analysis’ assessment should encompass the all stages of the drug development lifecycle and though it is not possible to accurately predict what MSLs will be doing in the long term, I have made an effort to outline some of these areas, broken down by drug development and launch activities, below:

• Horizon scanning

A major organisational capability will be to identify unmet medical need, particularly in chronic illnesses that by their nature are more profitable. MSL insights will be important and can bring the patient view, the HCP experiences, the available data, and key intelligence from conferences and other meetings, back into the organisation to enable strategic choices to be made. The insights may also identify competitor and potential strategic alliance partner activity in profitable disease areas. Knowledge management systems and external stakeholder engagement are integral to this capability so that identified unmet needs can be matched with scientific areas of interest, expertise, or under investigation. This is ‘bread and butter’ to MSLs and is unlikely to be carried out more proficiently by any other role in an organisation.

• Developing new products

Inventing, discovering or buying in of new products is core to the research-based industry. This capability will need to be leaner, reducing bureaucracy and allowing scientists to take the lead and be creative. MSLs are one of the more direct links between the scientists and the prescribers, especially in an organisation with few MSLs. The insights they bring in to the business, and the scientists in this instance, may contribute to the generation of new ideas for research and data generation. This collaborative approach could become the norm, particularly MSL discussions with horizon scanners which may lead to signposting of future areas for investigation.

• Clinical Trial Design

A systems approach will become necessary, so that trials are designed to meet the needs of the agencies that rule on Market Access guidance. There is also a trend towards the involvement of patients at an earlier stage of the drug development process. Communication with agencies in advance of research programme design, including health economic endpoints, understanding and including required genotypes for global approval, and adding patient reported outcomes will help avoid costly repetition of trials and delayed time to launch in different markets. In a large organisation there are likely to be specialists in these fields but MSL insights and knowledge transfer may benefit the participants in these discussions. If there is a standard internal process for CT design, there is a potential for MSLs to be integrated into this process, and contribute the ‘outside’ perspective, including the patient voice where appropriate.

• Legal and Patent expertise
A vital capability in an era of predatory generics companies, data protection, evolving technology and innovative pricing, tendering and contracting landscapes. MSLs may be called upon for provision of supportive data and general medical and scientific information to assist tendering, defending or bringing legal claims, and for advice or proof reading for legal and contracting purposes. Though uncommon, a working knowledge of legislation, tendering and ability to simplify complex concepts for a non-medical audience is a differentiator and sometimes underappreciated skill.

• Customer Engagement

The range of customers will require individual communication strategies and customer engagement will be a key capability. This is particularly so in the influential ‘key accounts’ such as large payer organisations, patient pressure groups, political influencers, Agencies such as NICE, and global scientific leaders. As the influence of individual prescribers wanes the need for large teams of sales reps will diminish and systems will need to be developed to compensate for the subsequent loss of customer and frontline knowledge. MSL communication and presentation skills are likely to be a differentiator in this environment, and MSLs must be proficient in these skills to be effective, continually challenging ourselves to improve.

• Marketing

Developing a ‘value proposition’ is a current activity of the marketing teams, and will be a more dynamic capability as they must adapt to the broader global and changing national markets. This will be based on customer needs and differing definitions of value. The MSL knowledge of treatments, competitors, pipelines, and supporting data will be invaluable in differentiation planning, and an opportunity to contribute at a strategic level. Knowledge transfer and education of commercial colleagues will continue to be a valued aspect of the MSL role, particularly to internal stakeholders.

• Operations Management

This is often a focus of efficiency measures, with implementation of programmes such as 6 Sigma, CRM, Lean and holistic systems approaches across various functions and organisations. In future it will be an important capability as quality management and efficient production, supply and distribution, particularly in new and evolving markets will be critical to operate in them successfully. The principles of these programmes may be useful in improving and standardising processes. Little of what MSLs do at an individual level, particularly activities that involve variables as diverse as HCPs, academics and scientists, can be formally standardised, but processes such as activity and insight reporting, and use of integrated CRM systems, can benefit from a uniform approach to implementation.

• Managing Reputation

Developing trust and a strong ethical reputation will be a critical capability, and the externally facing medical functions will be on the front line, engaging with diverse stakeholders, from patient pressure groups to policy makers, from scientist to prescribers. Trust in the data and how they are communicated is vital to acceptance of therapies in treatment pathways, formularies, health technology appraisals and patient information packaging.
Trust and reputation will also be critical in emerging markets as patients will be more likely to be the purchasers at least in the short term, and they will need to trust the brands. The MSL role is undeveloped in emerging markets and we might expect to see the experiences of UK MSL team development being leveraged for MSL recruitment in these countries. International career development opportunities will be enhanced if this situation arises.

• Combined service and product

As part of the value required by the NHS, particularly in a generics or tendering environment, add-on services may be provided. Some of these may be direct patient services, such as advice lines and home deliveries, whereas others may be indirect such as provision of data capture services to the NHS. As well as giving an improved service to the NHS there may be direct and measurable patient benefits, both disease-related and to patient satisfaction scores. Capabilities in both service and product provision will allow companies to operate as chronic disease managers should the landscape evolve in this way. MSLs would be in a position to enhance the value of the services with their knowledge of data capture, development of relevant endpoints, ethical utilisation of data, and using their insight of patient pathways and experiences to design the best add-on services.

• Market Access and Policy

Market access agencies such as NICE are subject to political and patient pressure, particularly in rare or emotive conditions, so there will sometimes be exceptions made to their cost-effectiveness thresholds. Where this is not a mass market, as in the case of rare cancers and orphan drugs, a niche strategy may be an option for small companies. There are potential opportunities for MSLs to operate in niche markets and companies, delivering a strategic and integrated cross-functionally supportive field/office hybrid role.

Conclusion

Healthcare and pharmaceuticals companies and their operating environments are undergoing a period of not easily predictable transformational change. New technologies and customers will lead to industry diversification and the adoption of new business strategies. Innovation and core competencies need to be implemented to improve activities at all stages of drug development and delivery to patients.

MSLs need to think strategically to understand how each of their activities and engagements with stakeholders contributes to the health of patients, the education of physicians, the research of academics, or their local, national or global organizational sustainability and growth. We need to know who we should engage with, which channel to use and when, what exchange is to take place, and what capacity, skills and knowledge we will need, aligned to each stage of the ‘bringing the drug to market’ process, to ensure the sustainability of the MSL role.

In a world where differentiation and prescribing decision making is often focused on cost and value, and not science and data, we need to understand and articulate what MSLs can deliver of demonstrable value to both internal and external stakeholders.
Well done on becoming an MSL! So now what?

A brief insight into my first three months of being an MSL

James Parker, PhD – New MSL

I started my new role as an MSL in July this year, with no prior experience. My PhD was obtained in Structural and Molecular Biology. After my studies I became a Senior Scientist at a small biotech and it was here that I first heard of the role of the MSL, instantly feeling that this was the encapsulation of everything I enjoyed with science, with outward facing responsibilities. After reading as much as I could about the role and the expectations, including how difficult it can be to obtain an MSL position, especially without experience, I set to work gaining as many transferrable skills and experience as I could. I moved internally at the biotech to a Business Analyst position.

This analyst position itself is not, on paper, anything like that of an MSL (desk based, non-customer facing), but the skills it does provide are that of actively seeking a deep knowledge and understanding of the field that you are working in, and the platforms and technologies that are being utilised. It helps to see how a clinical trial is designed and implemented allowing for critical evaluation of results. These skills are pivotal to the role of an MSL.

Once in the analyst position, with suitable time accrued I began actively seeking MSL roles. Reading and advice had taught me that without direct MSL experience, staying within a therapeutic area that you have experience in is the next best way of achieving your MSL goals, therefore I looked exclusively for oncology positions, having over 10 years of experience (including MSc and PhD projects). In total I submitted applications within a short time period to various large pharma companies. It took approximately 5 weeks from submission of the application to being offered a telephone interview. This interview was relatively short and was primarily to determine my motivations for becoming an MSL and how I felt the skills I had could be transferred to the role of the MSL. I was then offered an in person interview at what is commonly referred to as an “assessment centre”. The interview itself took the form of a 20 minute presentation, with a topic being provided to me, and a 60 minute competency-based interview. It only took 3 weeks to be informed of my successful application and the start date was agreed between all parties based on notice periods and other administrative timelines.

My first days at the company were filled with ‘On-boarding’. Being introduced to everything from HR and IT, to compliance, legal and pharmacovigilance (PV). It is here that I was provided with my IT equipment. As an MSL you will be a field based member of staff and therefore will spend the majority of your time working from home, when you aren’t meeting with healthcare professionals (HCPs) or key opinion leaders (KOLs), or in internal meetings with your team members. As a result of this you will be provided with enough IT equipment to set up your home office.

Another perk of being field based is being provided with a company car. My advice would be to choose wisely, you will be spending a lot of time in it and a safe, comfortable car should be a top priority. Once on-boarding was finished you will need to spend some time over the next week or two reading. There is A LOT of reading, and rightly so. Not only do you have to be fully up to speed with the inner workings of your new company, but also with the disease area you will be working in, and the specifics of the pharmaceutical agents that you will be working with. The company has a great policy of learning encapsulated by the 70:20:10 rule, whereby 70% of the learning you do is self-driven, on the job training, 20% is through internal training, sometimes from colleagues and team-members, and 10% is from official 3rd party courses that can be enrolled on. Take from this that you will be expected to read and learn independently, but that your team will also be a vital source of knowledge and information.
The learning is a continuous process to ensure that you stay on top of new developments both with the products you work with, and the field as a whole, but to ensure your knowledge meets the standard required by the team there is an internal validation process. This involves presenting a given topic internally to your team, who will critically evaluate your content and presentation style, including responses to questions. This is to determine your ability to deal with real-world examples of interactions with HCPs. Prior to this there are also opportunities to shadow existing MSLs to meetings, to get a feel for how these experienced MSLs respond to unsolicited requests for information and how they develop relationships with their HCPs.

After 3 months my validation process is imminent and I have met with several HCPs working in relevant disciplines. I have found the support from team members invaluable, each with their own styles and characters, all contributing to a highly functional unit, and I look forward to fully bringing my contribution to the team. The MSL role so far has been exactly what I had hoped it would be, and I would say to anyone who is waiting to make the jump, or for the right opportunity to present itself, please see this as advice to know what to expect in the initial time in your new role, and also as an opportunity to know valued transferrable skills to help potential applications in the future.

Ed. Comments:

Reader: if you have tips for new MSLs that you feel would be of use to help them please share! email us journalmsla@gmail.com

Thank you, James; great insight and 'heads-up' of what to expect for an aspiring MSL, well shared.
Hello dear friends

So once again it’s time for another instalment of my insight into the wonderful world of MSL-ing!

So what are we going to talk about today? Well let’s have a chat about the C-word: no I don’t mean CHRISTMAS, I mean CONGRESS!!!

Congress attendance is a big part of the MSL role: there you are in a foreign country with members of your European and Global teams and countless healthcare professionals. To make you a lean, mean, congress machine, I’ve included some of my top tips and lessons from my experiences:

1) Invest in some language lessons

OK, congresses are for an international audience and will generally be in English, but you have to GET to the conference centre first! Picking up “I would like to go to…”, “where is the…” and your P’s and Q’s can save for some red faces (and some angry Uber drivers)!

2) Master the metro

If your company is anything like mine, they will provide you with metro tickets, although be aware that it is unlikely to be a direct route to the venue. In order to make sure you don’t end up in the wrong side of town, take some time out to analyse the map before you get on your merry way (I will not confirm or deny that I have gotten lost guiding HCPs back to the hotel and ended up at a tourist location instead!)

3) Meeting points

Trying to organise a meeting with any of your HCPs at a congress can be like finding a needle in a haystack (in my case, an email stating “come find me” without a locality springs to mind!). My suggestion is to meet near the entrance to avoid the hoards en route to the different sessions, or perhaps in the poster hall (outside of poster exhibition times). Trust me, spending 30 mins going around the labyrinth which is the conference centre maybe great for your step count but no so much for being efficient!

4) Know the schedule

Big congresses will have a number of parallel sessions and, in lieu of human cloning, prioritising with your team for sessions in VITAL! Also, working out where the sessions are will save your time and your legs (the largest congress centre that I have been to was roughly the size of Heathrow airport!). Also, if there are any sessions that you really want to attend pop them in your Outlook calendar (congress apps are great, but I for one cannot cope with details in multiple locations: simplicity people!).

MSLAJ, Vol. 1 Issue 3 (December, 2018)
5) Plan outside of congress activities well

Congress days are LOOOOOOOONG: including morning sessions and company dinners, you are probably looking at 15-hour days. If you are anything like me and become a raging bull without their 8+ hours, I would strongly suggest working with your team to cover “shifts” (early, day and evening), so that you are not on the go for the full 15 hours. Also, whilst you’re in a new country try to take an evening or a free morning before congress commences to explore: your body and mind will thank you believe me!

Anyways that’s it for another edition from me: hope you guys all had a fab Christmas and I’ll see you next edition 😊

Hugs & regards,

Molly
MSLs and Remuneration: How does the ABPI Code apply? Dr Rina Newton, CompliMed

In October 2018, the PMCPA published a case (AUTH/2987/10/17, aspects of which are summarised in the table below) relating to the remuneration of MSLs at Shire.

The learning points affect how companies determine the bonus payments made to MSLs.

An anonymous, contactable, apparent ex-employee complained about Shire’s MSLs.

<table>
<thead>
<tr>
<th>Complaint</th>
<th>Response</th>
<th>Panel Ruling</th>
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<tbody>
<tr>
<td>Shire’s internal strategy allowed MSLs to target the numbers of visits and link this to their evaluation and possible bonuses.</td>
<td>Key performance indicators for the MSLs were balanced, ethical and appropriate. The MSL role was neither based nor measured on, promotion. Quantitative measures for HCP interactions was an <em>aspirational</em> measure only.</td>
<td>This breached the Code because: Aspirational targets for the number of visits made to KOLs (rather than % of visit requests completed) linked to MSL remuneration, was inappropriate. This might encourage behaviour inconsistent with the Code and therefore was poor standards.</td>
</tr>
<tr>
<td>The MSL role should be reactive regarding unlicensed products, not proactive.</td>
<td>No proactive unlicensed discussions took place, only ‘KOL engagement: through compliant scientific exchange’ i.e. only responding to unlicensed discussions, reactively.</td>
<td>This did not breach the Code because: No evidence had been provided to demonstrate proactive promotional discussions had taken place.</td>
</tr>
<tr>
<td>Shire showed a lack of respect for ethics and code of conduct [sic].</td>
<td>Shire denied all breaches.</td>
<td>This did not breach the Code because: The circumstances did not warrant a breach of Clause 2.</td>
</tr>
</tbody>
</table>

This case suggests that:
- The remuneration of MSLs must not be linked to the number of enquiries answered or number of HCP visits, meetings or sales in a particular territory.
- A bonus scheme linked to the *percentage* of enquiries or visit requests completed is acceptable for MSLs.
An Introduction to Reflective Practice and Personal Development Planning

Dr Sarah A. Goffin, PhD MFRPSI MRPharmS

Reflective practice has long been adopted within the healthcare professions as a way of recording learnings and showing commitment to adopting best practice. Whilst this is a mandatory process for those of us who also bear a healthcare registration, it is an extremely useful tool for self-development that could truly benefit both your overall competency in the role as well as potential future job prospects.

The key principles of reflective practice involve the following:

- Objectively identifying points of development
- Identifying the methods by which these points will be improved
- Identifying the pros and cons of different learning methods to be able to improve one’s skills
- Undertaking the aforementioned learnings and reflecting as to what further work needs to be done

Whilst some may argue that this in itself could be a laborious exercise, it is key to highlight that reflection is something that we as individuals do innately: if one thinks of a reflex action, say in terms of touching a hot surface, you pull your hand away and conclude that hot surfaces can be painful and hence that the action should either not be repeated, or repeated in a manner that permits some form of self-protection.

In our day-to-day working lives, we undertake a more conscious view of this process: particularly when starting out within the MSL role there are a plethora of different skills that need to be developed in order to effectively carry out the role: critical appraisal, statistics and communication skills to name but a few. I am sure that many of you undertake courses in order to improve your skills, however if this is not documented firstly that learning could be forgotten over time and secondly, the relevance and learnings of said development are not “proven in writing” (that is, it is possible to attend a session and get a certificate however this in itself does not necessarily demonstrate your understanding of what was covered and how you can adopt this within your work).

Where to Start?

There are four key areas within the reflective practice cycle:

- Planning
- Evaluation
- Action
- Reflection

It is key to note that this is a cycle and hence it is possible to start at any point. Below is further clarity on what each of the points in the cycle represent and the questions that should be considered for each one:

Planning

At the planning stage, a learning need has been identified. At this point, discuss what the learning need for improvement is and why, as well as a strategy for how to address this. Dictating the
rationale for this learning need will also help to prioritise it against other learning needs. In terms of how the learning needs can be addressed, there is a multitude of different approaches, with a few listed below:

- Reading publications or textbooks
- Attending seminars or workshops
- Accruing another qualification or completing e-learning modules
- Shadowing a colleague
- Being shadowed by a colleague
- Giving a presentation
- Leading a seminar etc

Each method with have pros and cons: some incidences may give practical experience, whilst others may only give a theoretical scenario. Some activities may also be more time-consuming or costly than others, which are also key factors to consider. It is also important to have goals as to when to undertake these activities to enable tracking of progress. Depending on the types and variety of activities to be undertaken, it is also possible to judge how this will affect your overall competency.

- The Miller’s pyramid is an example of how personal skill can be measured:
  - Knows (understands the theory, but no practical experience)
  - Knows How (heavily supervised practical experience/minimal practical experience)
  - Shows How (high degree of practical experience with minimal supervision)
  - Does (particular activity is undertaken routinely without supervision)

For those that struggle with this approach, the alternative is to create an ordinal scale of your personal ability and how these activities have enhanced this.

**Action**

This is the description of the activity or activities undertaken to reach the learning need. At this point, it is key to discuss what was actually learned from the experience (for example, there may have been a group participation element that may have also assisted with teamworking, which should also be noted).

**Evaluation**

Following on from what was discussed in actions, this is where the effect on future work would be documented. Leading on from this, it is the time to discuss how you plan to implement your new learnings and again potentially reviewing the pros and the cons of the activities undertaken to improve

**Reflection**

Has the learning need been met? If not, why? If starting with this point on the cycle, there may have been an event that has got you thinking about your learnings and whether or not further action needs to be undertaken to improve oneself. Sometimes, a learning need maybe fully met (such as learning how to ride a bike or drive a car), however more often than not there will still be further progress to be made at a later date, hence it is imperative that your reflective records be revisited periodically to determine if further learnings are required.
Just Say No - Deprescribing and Polypharmacy

Zeshan Ahmed - MSL

In the March issue of the MSLA journal, I talked about the growing prevalence of polypharmacy and the key factors fueling this growth. In this follow up piece we will delve deeper into the challenges arising from this, discuss deprescribing and how an understanding of polypharmacy and deprescribing is of value to the MSL.

The timing of this follow up article could not be any more apt as it coincides not only with a feature article published in the Pharmaceutical Journal\(^1\), but also the commissioning of an NHS review into overprescribing, to be led by Chief Pharmaceutical Officer Dr Keith Ridge\(^2\).

**Background**

Before digging any deeper, it would be helpful to gain clarity on what polypharmacy and deprescribing mean. Traditionally the term polypharmacy, as the literal meaning derives has meant the concurrent use of multiple medicines by one individual. This has usually been benchmarked at 4-5 medicines. However, such an arbitrary definition is not fit for purpose anymore; as such polypharmacy may be sub-divided and defined as either:

**Appropriate polypharmacy:**
Prescribing for an individual for complex conditions or for multiple conditions in circumstances where medicines use has been optimised and where the medicines are prescribed according to best evidence\(^3\) e.g. a patient suffering with heart failure, type 2 diabetes and hypertension, whereby his/her medication regimen has been rationalised and the prescriber has ensured that all medicines prescribed are evidence based and have a current and valid indication.

**Problematic polypharmacy:**
The prescribing of multiple medications inappropriately, or where the intended benefit of the medication is not realised\(^3\) e.g. the same patient as above, however this time their regimen has not been reviewed and their repeat medicine list contains several medicines with an unknown indication and/or redundant medicines which were prescribed for a one-off acute event but have remained on the patients repeat list and may be now causing side effects.

**Deprescribing:**
The process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes\(^4\). Deprescribing is not about denying effective treatment to people who will benefit, it is about ensuring people do not receive unnecessary treatment, which is unlikely to be of benefit and may cause harm\(^5\).

Clearly from the above definitions the problem lies with problematic polypharmacy, which can lead to adverse drug reactions (ADRs), falls, cognitive impairment, nonadherence, admission to hospital and death\(^2\). To add some context to this, up to 50% of medicines are not taken as prescribed. The rates of drug related hospital admissions quoted in literature vary widely, from 6-10% and over 70% of ADRs are avoidable\(^5,6\).

By background I am a clinical pharmacist and have experienced firsthand the associated complications arising from problematic polypharmacy and have also participated in pharmacist led polypharmacy medication reviews and wider MDT meetings to this end. No doubt, two of the most common problems I have encountered in practice are nonadherence and ADRs. The pill burden on a patient is negatively correlated to their adherence – the more medicines a patient is prescribed the greater the likelihood of nonadherence.
Prescribing is the most common patient-level intervention in the NHS and is the second highest area of spending in the NHS, after staffing costs. Doctors are trained to diagnose and prescribe the appropriate treatment. Hence, it is not difficult to understand how the idea of “deprescribing” has faced many challenges. Inherently it goes against the training – there is no class in medical school on “stopping medicines”. Furthermore, from my experiences as a pharmacist I have seen these challenges in practice. On one end of the spectrum there is the patient and their family – who can over time become very attached to their medicines, any cessation of drugs can invoke emotive responses; in some instances, family members may feel that their loved one is no longer being cared for appropriately, that the doctor has “given up” on them. On the other hand, we have the prescriber, they face the challenges of stopping medicines in the absence of clear guidelines on deprescribing. There is a paucity of published evidence to support the cessation of medicines. In addition to this, where a medicine has been commenced by a more senior clinician, there is a greater reluctance to question and/or stop this – “if ain’t broke then don’t fix it”.

The result of this cocktail is often an unchecked, unchallenged list of medicines which are prescribed to a patient for a given event at a time but then migrate over to the patients repeat medicines list, where they can linger on for years unless reviewed and questioned. A classic example of this is a patient admitted to hospital for an acute event, during this admission they are prescribed a proton pump inhibitor (PPI) to protect against any adverse effects from their anti-inflammatory analgesic. After a one week stay, the patient is treated and discharged home, the anti-inflammatory analgesic for which the PPI was prescribed is no longer needed and stopped. However, the PPI finds itself a new home on the patients repeat medicines list and here it can remain for several years unchecked. Long term adverse event of PPIs includes increased risk of fractures (especially in the elderly), an increased risk of clostridium difficile infection and masking of the symptoms of gastric cancer. This is purely an illustrative example to help explain how problematic polypharmacy can grow organically.

Where does the MSL fit in?

So where does the MSL fit into this discussion? What role can they play? Is there even a role to play?

Rewind the clock 12 months back and I would not have had a clear answer for the above questions, my opinions and experiences would have been shaped solely from the lens of a clinical pharmacist. Fast forward to the present, having been an MSL for almost a year I can now certainly add a different perspective to the debate.

The past year as an MSL has been to say the least a whirlwind of an experience. Having had the opportunity to speak with various clinicians, attend congresses, gather insights and converse with colleagues from different therapy areas has enabled me to observe the similarities that exist across therapy areas. One common thread that I have found come up time and time again, is the topical issue of adherence or nonadherence shall I say. This is something which seems to transcend boundaries and affects patients across all specialties of medicine. Understandably so, ensuring a patient correctly takes their medicine as intended is fundamental to ensuring they derive the maximum benefit from that medicine. Furthermore, the MSL has a responsibility to ensure that their company’s medicines are utilised effectively and appropriately, as to maximise patient benefit. As such, nonadherence is a barrier to medicines optimisation and certainly this is one topic that appears at almost every conference.

The core function of an MSL is to build collaborative relationships with KOLs, in doing so we are afforded much insight into the local challenges faced by these clinicians in their daily practice. To be a successful MSL is to be the one who can understand and appreciate these challenges, to utilise the insights gathered and present solutions and improve patient outcomes. Just as we need to understand the NHS and its inner workings, from structural reforms to financial constraints
in order to fully appreciate the environment of the KOLs with whom we are building a relationship with; similarly, MSLs from all therapy areas should be aware of the direct and indirect impact of polypharmacy on the patient AND the clinician. Especially from the perspective of adherence to medicines - how does the clinician deal with nonadherence? Do they attempt to rationalise their patient’s medication regimen?

As an MSL you will likely be dealing with specialists and in such cases the likelihood of the Consultant/Surgeon having the time or scope to explore the patients “other” prescribed medicines will be limited; such a holistic approach is more likely to be found in primary care by GPs. One factor adding to the problem is that of a patient with say three medical problems, seeing three separate Consultants. Each Consultant is looking after their “medical problem” and prescribing accordingly. Issues can arise when the lack of cross-communication between medical specialties leads to concurrent drugs interacting and causing ADRs. Understanding the dynamics of this type of situation can be a valuable insight for an MSL.

A lot has changed from the time when I first dipped my toes in the waters of polypharmacy medication reviews. Back then there was a scarcity of not only pharmacists working in this area but also published literature detailing the problem and resources to help address it. Now, a simple Google search of polypharmacy/deprescribing will bring up a plethora of search results including NICE guidelines, a report from the Kings Fund, several BMJ articles and some excellent medication review resources produced in Scotland and Wales. I would urge all MSLs to have a look at some of these.

Problematic polypharmacy has an adverse impact on a patient’s adherence to their medicines. This is something that clinicians are dealing with daily in the NHS, it is not a local challenge rather a national, global medical burden. MSLs should have a basic understanding of this relationship. At the very least, they will be better equipped to converse with their KOLs and understand the problem. At the very best their credibility as a trusted peer will improve, especially if the MSL is able to bring forth potential solutions.

References:
1. Pike H. Deprescribing: The fight back against polypharmacy has begun. The Pharmaceutical Journal. 2018; 301 (7919): 279-282
The journey to my first MSL interview

By Sadiq Rafiq Ahmed, MPharm

Applying for a job is never easy. Your mind can often put up barriers, trying to give you any excuse not to do so. Am I good enough? What if I fail? Have I got the time or energy to go through with this all? Trying to jump these hurdles can be a challenge in itself, let alone the actual process of applying. Usually, we try and step up the ladder within our career path, going for that sought-after promotion. But what about applying for a completely new role? This can be even more daunting, requiring more preparation and meditation to get your mindset right for the challenge ahead. As a pharmacist who has worked in multiple healthcare sectors, I attempted to make the leap to the pharma industry to work as a Medical Science Liaison. I will be going over my experiences and what I have learnt from this process, and hopefully give aspiring MSL’s a push to get that role.

The first step of applying for an MSL role is to get your CV perfect and nail the job application. I went through the job description and tailored my personal statement to meet the requirements of the role and ensure that I had defined examples which show that I have acquired skills that can transfer to the pharma industry. It is important that time and care is given to every application and the meet the needs of your prospective employer.

An important tip in improving your chances is networking. I used LinkedIn to reach out to a few individuals with a similar career to mine who were able to get a job as an MSL. They were kind to spend a few hours talking to me to give a true idea of the life of an MSL, what their thoughts were and how they got their jobs. This will give you an insight to the role and make sure it is the right decision for your career. My passion for the role strengthened from this and helped me to convey it in my application and interview.

I was able to land an initial phone interview with the HR advisor. This was a simple conversation, just to find out if I know what an MSL role actually is and why I think I am suitable for the role. This is not a difficult call, and it’s not there to trip you up. The main aim is for them to know you understand the role you are applying for.

I have been interested in an MSL role for quite some time but to really sell myself, I had to dig deep and find out why I wanted to do this, and make sure that when questioned, I can portray the reasons for doing so. This is an important step that I encourage all individuals to do as the interviewer will be looking to see a genuine response.

I had another phone interview with the hiring MSL manager, which was again quite a simple interview. He asked me about what I have been doing so far and some simple questions about the role. The purposes of these two phone calls are to ensure that potential candidates are truly dedicated to getting this role and your understanding of the role and motivations need to be confidently communicated.

I have been previously successful in traversing across the different pharmacy sectors such as community, hospital and primary care/commissioning, so I thought if I can get those jobs, I can get this one too. A positive mindset is absolutely essential as you need to be confident in your interviews. My past experiences have shown that you need to be a natural communicator and be able to have a conversation rather than it be like an interrogation.

When I was emailed to attend the final face to face interview, I had a massive challenge ahead of me. The interview was scheduled in the morning over 100 miles away and happened to be on the day after my final assignments were due for a postgraduate course I was doing! Preparation for
the interview was intense, which included presenting trial data, revision for a quiz and practicing the competency-based questions that I would be asked in the interview. Juggling this with my coursework was indeed difficult, along with full time work and a family to take care of, it felt like an impossible task. The take home message from this is that the interviews may be at a very difficult time in your life. There is seldom a perfect moment but this shouldn’t put your off. Work harder than you ever have, and don’t be shy in telling your interviewer how you overcame all odds to be there at the interview.

A tip that many other MSL’s gave me was to stay in a hotel the night before the interview. I would highly recommend this to all aspiring MSL’s who have an interview far away, as it will take the stress of travelling from your interview and will ensure you have a good night’s rest. This may cost a little bit but this is an expense worth making.

The interview was a fantastic experience. It was thorough and challenging but was honestly something I enjoyed. I was able to converse with three senior staff and had the opportunity to explain how much I wanted this role. When I left the interview, I was really happy with my performance. I felt that I answered the questions confidently and my presentation went smoothly. There were some questions that I was asked about the trial that I didn’t have the answers to but there is no shame in politely saying that you don’t know. The important thing is you don’t make up answers and you ensure you state that you can find the answer from an appropriate source.

I was informed in the interview that it would be a few weeks before I got an answer if I was successful due to other interviews that were still to happen. As a reflective individual, I replayed the interview over and over again in my head, which is probably good to a certain degree, but this can be detrimental as I was starting to critique all of my answers. This can have an negative impact on confidence, so to help mitigate to this, I took pen to paper and wrote out all the questions I was asked. This exercise helped me to let go from the experience and also will help me in future interviews as I will have a bank of questions that I can prepare from.

Unfortunately, I did not get the job. I was disappointed of course, but I was happy that I had got this far. I spoke to the HR advisor to get feedback, which is essential to improve your interview performance. To my surprise, my feedback was glowing. There was no negative feedback, nothing to improve on and I was actually their second choice, only to be bested by an individual with MSL experience! I was so pleased with this feedback. This was only my first interview and given that I have no prior MSL experience, I still felt that this was an achievement.

So what next? I was suggested to do this reflection piece to help other professionals get into the MSL role. It is always helpful to hear from someone else in your shoes and I hope that my experience helps someone out there. Just keep applying, prepare well, network and most of all, be confident.

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*Ed: Thank you for sharing Sadiq. The journey can be long and arduous, but as many an MSL will tell you, it’s worth it. Best wishes.*

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Becoming an MSL – The CV: Finding your Voice

Andrea Litovszky and Jon Elliott from AXESS Ltd

For those of you unfamiliar with the TV music talent show “The Voice”, contestants sing to four coaches who have their back turned. The premise is if the coaches like the sound of the singer, they press a button on their chair and turn around to face the singer. Their view: It’s all about the voice. For the singer they need to choose the right song to suit their voice to get a coach to hit that button.

Now you probably see where this is going. Reimagining the above scenario, you are the singer, your song choice is your CV, and the coaches are the recipient of your CV. The Voice of the CV is how you put yourself across in the best light.

Firstly, ask yourself the question: What is the aim of your CV?

Like the above anecdote your CV needs to turn heads and secure you an interview. Recruiters/ hiring managers/ HR departments all receive high volumes of applications so you need to make yours stand out.

Here are the AXESS top tips to writing your CV to secure that interview:

The two most important aspects of a well-written CV are

Content                   Presentation

CV Content

**Name & contact details** – Use the name that you are known by, rather than your given name, if different, and make sure your contact details are listed and correct. If you are open to re-location, it is worth to indicate it in this section.

**Brief synopsis of experience and career aims** – aka The Hook
This should be about three lines and the aim of the profile section is to highlight your Unique Selling Points (USPs) and career aspirations. It is vital to keep it relevant and in line with the responsibilities of the role you apply for.

**Employment** – This should be presented in reverse chronological order, with the greatest amount of information given for the most recent or current position. Focus on your achievements and key skills, especially “transferrable skills” if you are applying for a role you have never done before. Use past tense to convey that you have actually done what you are writing and use positive affirmations and adjectives to emphasise your achievements. Reason for leaving can be discussed during an interview so it is not necessary to indicate but if there are gaps in your employment, it is worth explaining them, e.g. Career break to go travelling, family reasons (no further details required here).
**Education** – Education & Qualifications should be presented in reverse chronological order as well, and should clearly state the name of each qualification, the establishment, and the relevant dates. If your dissertation thesis is therapeutically aligned with the role you are applying for, mention the title as it can further strengthen your application.

**Specific skills** – The content and size of this area will depend on the specialisation in which you are working. You should identify any particular therapeutic expertise, management experience, I.T. Skills or relevant training.

**Additional information** – This section allows you to add information on interests and non-work related achievements. Bear in mind that this section should be brief and concise and try to avoid generic pastimes such as “reading, shopping, and socialising”.

**CV Presentation**

When people are reviewing CVs they tend not to notice if a CV is particularly well presented, but they definitely remember if it is presented badly.

- Keep the document as plain and simple as possible, avoid borders, colour, fancy graphics, photographs and company logos
- Be consistent with your formatting, use simple typeface and readable font size. Ensure uniformity with date formats and indicate month and year for both education and employment.
- Send as a Word document to ensure that the formatting is not corrupted – agencies and clients also find these easier for their databases.
- Use spell check and proof read your CV before sending it and ensure that your LinkedIn Profile is in line with your CV.

**To Summarise**

The aim of the CV is to generate interest and get you an interview. To accomplish this objective, it has to highlight your relevant experience, achievements and transferable skills. It is important to keep it short, ideally no more than two to three pages and the content should be aligned to the role you are applying for. Offer specific examples, numbers and details, try to avoid generic statements or copying your current job description. This is your passport to the new role; it should reflect YOUR capabilities, competencies and what you can bring to the role.

It is worth keeping a copy of each tailored CV to take with you to any potential interview and a list of roles and companies you applied for, not only to keep track, but also to avoid duplicating your applications.
Understanding Subgroup Analyses in Randomised Clinical Trials

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This article is a partial summary of the content of the much commended MSLA ‘Statistics for MSLS; Subgroup Analyses’ Masterclass delivered by Professor Hackshaw earlier this year.

Purpose of Subgroup Analyses

Subgroup analyses are commonly performed by investigators of randomised clinical trials, and are reported in journal articles, often requested by reviewers or editors. Such analyses involve examining whether the effect of an intervention differs between patients with different characteristics or disease features. For example, Drug A could be beneficial in males but not in females. Because subgroup analyses are now an expected part of analyses associated with clinical trials, the purpose behind them has often been lost, and hence there is a potential for misinterpretation.

Subgroup analyses were largely exploratory and hypothesis-generating when they were first applied many years ago, but they are increasingly used to make recommendations for clinical practice, including as part of health technology assessments (HTAs) of new drugs. Subgroup analyses are now the core method of assessment for personalised medicine research, in which a biomarker or imaging marker is used to select which patients receive a certain treatment and which would not. They therefore contribute to marketing authorisation for new therapies (for example having oestrogen-receptor positive tumours for hormone therapies for breast cancer; or having high PD-1 or PD-L1 expression for immunotherapies).

Outcomes of Subgroup Analyses

There are four possible outcomes from subgroup analyses, and each require careful consideration:

1. The size of the treatment effect (benefit) is similar between different subgroups (i.e. no subgroup effect).
2. The treatment is effective in all patients, but the size of the benefit is noticeably greater in one group than another.
3. The treatment is effective (beneficial) in one group of patients but has no effect in another group.
4. The treatment is effective in one group of patients but is harmful in another group.

The first of these is the most commonly seen outcome in trials. It essentially provides some assurance that a new therapy is similarly beneficial across patients, so using subgroup analyses for this purpose seems reasonable. The second provides useful scientific information about the size of the benefit of a therapy but might not have impact on policy because all patients should still receive it. However, this information might matter when treatment costs are taken into account and the health economic
analyses are much more favourable for the group in which the treatment has the biggest benefit. In this situation, policy makers such as HTA agencies might only recommend use of the therapy for that particular patient subgroup, but it should be understood that this decision is driven by financial costs rather than clinical effectiveness. The last two potential outcomes of subgroup analyses have a direct impact on policy and patient care, because by definition some patients will receive the therapy and others will not. These are the outcomes that require very reliable evidence.

**Statistical Tests**

Most subgroup analyses are presented as forest plots, on which there are several/many factors. For example, in a trial of empagliflozin for type 2 diabetes, 15 factors were shown on the forest plot. Investigators should ideally pre-specify which factors they are interested in within the trial protocol, but during the course of an often long clinical trial other important factors may come to light, so it is reasonable to include these too when scientifically justified.

Many investigators do not realise that there are two different statistical tests for subgroup analyses. They are illustrated in Figure 1. One test involves comparing whether the treatment effect in each subgroup materially differs from the overall effect (formally called a heterogeneity test, and is similar to that used in meta-analyses). In some forest plots, this is easy to do because the investigators have drawn on a vertical line which represents the overall treatment effect seen in all patients, as well as the vertical line for no effect (e.g. relative risk or hazard ratio of 1.0). In Figure 1b, the overall effect is 0.90. We then see whether or not the 95% confidence interval for each subgroup for age overlaps (includes) 0.90. For patients aged >50, the interval is 0.70 to 1.10; and for those aged ≤50 it is 0.75 to 1.15. Both clearly contain 0.90; hence there is no evidence of a subgroup effect using this particular test. Another way to think of this is to remember that confidence intervals give us an idea of what the true effect of an intervention is likely to be. If the true effect for people aged >50 could be a relative risk of 0.90, and the true effect for people aged ≤50 could also be 0.90, then there is a possibility that the true effect is the same between the different age groups. In Figure 1a, both confidence intervals exclude the overall effect of 1.05. We therefore see whether or not the 95% confidence interval for each subgroup for age overlaps (includes) 0.90. For patients aged >50, the interval is 0.70 to 1.10; and for those aged ≤50 it is 0.75 to 1.15. Both clearly contain 0.90; hence there is no evidence of a subgroup effect using this particular test. Another way to think of this is to remember that confidence intervals give us an idea of what the true treatment effect is likely to be. If the true effect for people aged >50 could be a relative risk of 0.90, and the true effect for people aged ≤50 could also be 0.90, then there is a possibility that the true effect is the same between the different age groups. In Figure 1a, both confidence intervals exclude the overall effect of 1.05, so there is evidence of a subgroup effect. Generally, only one of the confidence intervals need to exclude the overall effect before we considering that there is a real subgroup effect.

The vertical line for the overall effect (hazard ratio for cardiovascular disease) is shown in the forest plot for the EMPA-REG trial, but not in the LEADER trial publication (Figure 2 in both articles), even though both studies were published in the same journal and within a year of each other. This illustrates that there is no standard approach for presenting forest plots. However, in the LEADER trial paper we can easily draw on the overall effect line by hand using a ruler. In both trials, every 95% confidence interval overlaps the overall effect, which means no subgroup effects (except for renal function in the LEADER trial). This overall effect line is actually important. Without it, people can make the mistake of comparing each subgroup effect against the no effect value. In Figure 1c we see that the 95% confidence interval for patients without systemic symptoms excludes 1.0 (statistically significant), whilst that for patients with symptoms includes 1.0 (not statistically significant). This appears to be an intuitive approach. However, by comparing each subgroup result with 1.0 ignores that we already have an estimate of the true treatment effect (relative risk 1.11). So the relevant question is actually whether each subgroup effect differs from the overall effect.

In a trial of an anti-cancer therapy (decitabine), the forest plot (Figure 3 of the article) does not have the vertical overall effect line, and the investigators seemed to have compared each subgroup factor against 1.0. They then comment that the benefit of the drug was more clearly shown only where the result excluded the no effect value of 1.0 (e.g. patients aged ≥70 years, performance status 2, and intermediate risk). But when adding on the overall effect line by hand (hazard ratio 0.82), this line cuts through all of the confidence intervals, so there is actually no subgroup effect for any factor.
The second statistical test is often shown on forest plots as the ‘P-value for interaction’. The interaction test compares whether the treatment effect is different between the subgroup levels. Both trials of type 2 diabetes mentioned previously show these p-values. This test is quite different to the heterogeneity test described above which assesses whether the effects in the subgroups differ from the overall effect. In Figure 1a, the interaction p-value tests whether the relative risk for males (1.56) is really different from that for females (0.71). The p-value is small (0.004), which indicates that these two relative risks are statistically significantly different from each other; hence evidence of a subgroup effect. Whilst in Figure 1b, the interaction p-value is 0.73, so the relative risk of 0.88 is not materially different from 0.93 (no evidence of a subgroup effect). In a review of 221 oncology trials (published 2011-2013), 85% reported subgroup analyses, but among 102 studies claiming subgroup effects only 18% were supported by statistically significant interaction tests. The interaction p-value is required for personalised medicine trials. In a trial of panitumumab for advanced colorectal cancer, the hazard ratio for overall survival (panitumumab + standard chemotherapy versus chemotherapy alone) was 0.83 for patients with KRAS wild-type tumours and 1.24 for KRAS mutation-positive tumours. The interaction p-value was <0.001, strong evidence for a subgroup effect (i.e. that 0.83 is statistically different from 1.24). The conclusion and hence the marketing authorisation for panitumumab was to use it for KRAS wild-type tumours only.

Interpretation of Tests

Researchers should be clear about which of the two statistical tests they wish to examine and interpret, given that the interaction and heterogeneity tests have a different purpose. This is
important because they can give inconsistent conclusions. In Figure 1c (based on a published trial), the hazard ratio of 1.76 is statistically significantly different from 0.81 (p=0.025); which is evidence of a subgroup effect using this test, i.e. the experimental drug could be harmful in patients without systemic symptoms. However, when we compare the confidence intervals against the overall effect (hazard ratio 1.11), both include this value; hence no evidence of a subgroup effect using this test.

If subgroup analyses are to be used to decide which patients receive a certain treatment and which do not, we ideally need very reliable evidence for this. Hence, both statistical tests should be met. First, subgroup effects should be examined in relation to the overall effect. If there is evidence of heterogeneity (heterogeneity test p-value<0.05), then use the interaction test. This approach should provide the strongest statistical evidence for subgroup claims than either test alone. An exception might be where the interaction test indicates harm in one subgroup whilst the heterogeneity test is borderline (as in Figure 1c), so the decision might err on the side of caution and conclude a real subgroup difference to avoid giving a potentially harmful therapy to some patients.

**Further Subgroup Analyses Considerations**

In addition to these two statistical tests, investigators need to consider the following issues:

- Dividing the whole trial into subgroups means that each subgroup is based on fewer patients and fewer events, and often very few events; so the reliability of the analyses could be low.
- Splitting the data into subgroups can undo the balance achieved by randomisation, leading to confounding and so the interpretation of the treatment effects could become more complicated.
- Having many subgroup factors is a form of multiple comparisons, which can lead to spurious findings. Investigators sometimes perform numerous subgroup analyses, particularly when no overall effect is found, with the intention of finding a ‘positive’ effect somehow. The more factors examined, the higher the chance of finding a spurious effect. This is well illustrated in a large trial of aspirin and myocardial infarction, in which the investigators conducted many subgroup analyses to show that aspirin was ineffective among patients with a Libra or Gemini astrological star sign but beneficial among all other star signs. Both statistical tests for subgroups would be met in this example, but clearly there is no biological sense to this subgroup effect.
- The star sign example implies that biological plausibility for the subgroup effect should be an essential consideration before recommending some patients receive the treatment whilst others would not. But investigators need to be aware of creating a scientific explanation only after seeing the subgroup results.
- If the subgroup effect appears real (statistically significant and with biological plausibility), there should be independent corroboration from other studies.

In the context of HTAs, subgroup analyses can represent a real challenge for both policy makers and investigators. Sometimes, the HTA agency requests subgroup analyses, which are not pre-specified, and the issue of multiple comparisons arises. Naturally, investigators including commercial companies wish their therapy to be used by as many patients as possible, for whom they believe would benefit from it. But with limited public funds in many healthcare systems, this might not be cost-effective hence why recommendations can sometimes be for the therapy to only be used in certain patients. In which case is it better to get some form of HTA approval for some patients or outright rejection for all patients? The answer is perhaps obvious. But then both parties should acknowledge the potential for some patients not receiving a beneficial treatment.

**Conclusion**

Performing subgroup analyses is routinely done now, and this situation is unlikely to change, despite their unpopularity among some researchers because of the pitfalls outlined above. Fewer trials are generally being conducted using the same therapy for a particular disorder, so it is important that subgroup analyses are carefully interpreted, especially when subgroup claims may
not be supported by a sufficient number of other studies. However, one of the main values of subgroup analyses, to show that a treatment is similarly effective across different groups of patients, is something that remains appealing.

References


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