

# Switch management between similar biological medicines: A communication information guide for nurses



## FOREWORD

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This information and communication guide on the safe and efficient switching between similar biological medicines addresses a highly relevant issue with healthcare professionals and patients and is an example of cooperation in an interdisciplinary context.

Today's nurses, with their increased knowledge and experience, play a major role in sharing responsibility; in some countries they have prescribing authority in close cooperation with physicians. Developing the patient Q&A on biosimilars and taking the initiative to establish an efficient communication document for nurses, patients and physicians, bear witness to this.

Nurses are now high-level professionals tackling the current and future challenges side by side with physicians. This phenomenon is welcomed by patients and evidence has shown that users and consumers are very satisfied with this new and shared responsibility.

The importance of education is paramount in improving the efficiency of healthcare and addressing the growing use of IT and E-health as well as the increased expectations of consumers, patients and healthcare professionals.

This educational and practical guideline indicates the shared interest in good switch management in the use of biological and biosimilar medication.

Evidence based on collective experience at all levels, this guideline will serve patients and physicians and, above all, nurses when confronted with the terms biosimilar and switching.

For those new to biosimilars, having a useful guideline such as this, in a nurse's narrative, will prove an essential aid when communicating with patients and other healthcare professionals. It is an excellent tool for ensuring the best possible care for patients during switching of their biological medication.

I fully recommend this guideline, which is both educational and practical, to read and above all to use without hesitation.

Pascal Rod

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DRAFT

# 1 INTRODUCTION

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This information and communication guide for nurses is designed to provide support and information for nurses working with patients who are switching between similar biological medicines – this could be a switch between the original biological medicine (known as the reference product or the originator product) and a biosimilar medicine (or vice versa), or between biosimilars of the same original medicine.

The guide provides examples of projects and best practices based on different specialities to increase trust in biological medicines including biosimilars. Its aim is to contribute to the safe use of and trust in biological medicines, and to give nurses the tools to implement switching decisions in a clinical context and deal with patient concerns, drawing on the learnings from real-life experiences.

One of the most important elements in nursing is the relationship between the patient and the nurse. As frontline professionals, nurses play a key role in supporting communication between patients and physicians, especially when treatment regimens and medications are initiated or changed. Their experience and their communications skills mean that they are ideally placed to explain to patients about the rationale and impact of changes to their treatment. This can be particularly important in the transition from the originator biological medicine to its biosimilar form (and vice versa).

While the physician is most commonly the authorised prescriber, nurses can take the lead in implementing the transition between branded and biosimilar biological medicines. This includes managing the process before, during and after the switch. However, this isn't the case everywhere, and the role and responsibility of the nurse can vary between hospitals, regions and countries. For example, in the Netherlands, specialist nurses can prescribe within their own speciality.

The European Commission and European Medicines Agency (EMA) have created a [patient Q&A on biosimilars \[1\]](#) and a [guideline for healthcare professionals \[2\]](#), and these publications will provide further information on this important issue.

## 1.1 REFERENCES

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2. European Medicines Agency and European Commission. *Biosimilars in the EU: Information guide for healthcare professionals*. Created: 2017. Available from: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Leaflet/2017/05/WC500226648.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf).

## 2 INFORMATION ABOUT BIOLOGICS, INCLUDING BIOSIMILARS

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### 2.1 WHAT ARE BIOLOGICAL MEDICINES?

Rather than being synthesized chemically, biological medicines (including biosimilar medicines) are produced from living organisms, such as mammalian cells, bacteria or yeasts. Biological medicines are usually larger and more complex than chemically-synthesised compounds.

As defined in 'Biosimilars in the EU: Information guide for healthcare professionals' [1]:

*Biological medicines... can have an inherent degree of minor variability ('microheterogeneity'). This minor variability must fall within the acceptable range to ensure consistent safety and efficacy. This is done by adjusting the manufacturing process to guarantee that the active substance fits into the desired specifications range.*

*This degree of minor variability can be present within or between batches of the same biological medicine, particularly when manufacturing processes are modified during the commercial life of the medicine (e.g. increasing production scale). Strict controls are always applied to ensure that, despite this variability, there is batch-to-batch consistency and that the differences do not affect safety or efficacy. In practice, variability (within a batch or batch-to-batch) is very low when using the same manufacturing process.*

### 2.2 WHAT ARE BIOSIMILAR MEDICINES?

As defined in 'Biosimilars in the EU: Information guide for healthcare professionals' [1]:

*A biosimilar medicine is a medicine highly similar to another biological medicine already marketed in the EU (the so-called 'reference medicine'). Companies can market approved biosimilars once the period of market protection of the reference medicine expires (after 10 years).*

*Due to the natural variability of the biological source and to the manufacturing process unique to each manufacturer, minor differences can occur between the biosimilar and its reference medicine and between batches of the reference medicine. Strict controls are always in place during manufacturing to ensure that minor differences do not affect the way the medicine works or its safety. Thus, these differences are not clinically meaningful in terms of safety or efficacy.*

#### FAQ 1: Is my medicine a biosimilar?

- A healthcare professional can check section 5.1 of the summary of product characteristics (SmPC) and can tell you whether your biologic medicine is a biosimilar or not.
- If you want to know more, the European public assessment reports (EPAR) on the [EMA website](#) have more information on individual biosimilar drugs.

Table 1: Specific features of biosimilar medicines	
<b>Highly similar to the reference medicine</b>	The biosimilar has physical, chemical and biological properties highly similar to its reference medicine. There may be minor differences from the reference medicine which are not clinically meaningful in terms of quality, safety or efficacy.
<b>No clinically meaningful differences compared with the reference medicine</b>	No differences are expected in clinical performance. Comparability and clinical studies that support the approval of a biosimilar confirm that any differences will not have an effect on safety and efficacy.
<b>Variability of biosimilar kept within strict limits</b>	Minor variability is only allowed when scientific evidence shows that it does not affect the safety and efficacy of the biosimilar. The range of variability allowed for a biosimilar is the same as that allowed between batches of the reference medicine. This is achieved with a robust manufacturing process to ensure that all batches of the medicine are of proven quality.
<b>Same strict standards of quality, safety and efficacy</b>	Biosimilars are approved according to the same strict standards of quality, safety and efficacy that apply to any other medicine.

Source: EMA and EC [1]

### FAQ 2: Why are you changing my current treatment to a biosimilar medicine?

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- There is now at least one other company producing your biological medicine as the patent on the original version has expired. The biosimilar has the same therapeutic value as the original medicine but may be more cost-effective, and is equally safe and effective.
- This means that we can be confident we can keep you on this treatment for as long as it works for you.
- The better cost-effectiveness may mean that we can give you and other patients access to a wider range of medicines, which may be able to help you if we need to adjust your treatment in the future.
- We may also be able to provide you with better support at home and in hospital in the future if using the biosimilar means that we have more money available.
- If you have to make a co-payment on your medicine, this may be lower for the biosimilar.

There have been many studies comparing the efficacy and safety of reference biologic medicines and biosimilars, and on the chances of biosimilars triggering immune responses. These confirm no changes in safety and efficacy, and no increased risk of immunogenicity [2].

### FAQ 3: How do you know that biosimilar medicines are safe?

- In the European Union, every medicine that you are given has been reviewed and authorised according to Community law.

- The European Medicines Agency (EMA) carefully assesses the safety of all medicines it approves and requires ongoing monitoring of adverse events that could be associated with use of the medicine. If a biosimilar is approved by the EMA, you can trust that it has undergone a rigorous assessment of its safety and efficacy.
- When a new medicine is approved by the EMA, the Agency also publishes a summary for the general public, explaining why the medicine is approved in the EU, and what studies have been carried out to show that it is safe. These summaries (called 'EPAR summaries'), are available on each medicine's landing page on the [EMA website](#) in the form of question and answer documents in all official EU languages. EPAR summaries for biosimilars can be accessed by searching for the medicine's name on EMA's homepage.
- Your country's national regulatory authority will also provide information on biosimilars in your local language.

The development of a biosimilar may take up to 10 years and cost up to € 250 million. This is often not as high as the development of new medicines. Because of their availability, biosimilars result in greater physician, patient and payer choice, and can be less expensive than reference biologic medicines.

#### FAQ 4: How do you know it's as good as the original medicine?

- Your biosimilar medicine will only be approved by the EMA if it has been proved to fulfil the same quality requirements and to be as safe and effective as the original medicine.

#### FAQ 5: The biosimilar is cheaper. Doesn't that mean it's not as good?

- The biosimilar and reference biologic medicine that you have been prescribed are the same molecule.
- The same rules and rigour are used to authorise all medicines in the EU and all biological medicines (both reference products and biosimilars) approved by the EMA are safe, effective and of high quality.
- Developing biological medicines (reference products) is very costly, and requires important research budgets and a range of stringent clinical trial data. The rate of failure can also be high. To cover these efforts and investment costs, the newly developed medicines are protected by patent for a predefined time. After patent-expiration, the market is open for biosimilars. They help to make research progress affordable for the health system in the long-term.
- Companies developing biosimilars need to prove they have the same safety and efficacy as the reference product, but do not need to repeat all the clinical studies, and so the investments are lower.
- Because you are being treated with the most cost-effective biological medicines, you could benefit through reinvestment in patient care.
- Because we use the most cost-effective biological medicines, more patients can be treated or can gain better access to supporting therapies, or they may be able to get earlier access to treatment.

- We may also be able to provide you with better support at home and in hospital in the future if using the biosimilar means that we have more funds available.

As every pharmaceutical company uses its own living organism pathway to produce the biological medicines, and because biological medicines have a very complex structure, there will be slight differences between the original product (the reference product) and the biosimilar, and therefore, biosimilars are described as 'highly similar, not 'identical'. Before they are approved for use in patients, biosimilars are tested to make sure that these small differences do not affect the effectiveness and safety [2].

### 2.3 USING THE SAME BIOSIMILAR FOR DIFFERENT DISEASES: EXTRAPOLATION OF INDICATIONS

Since a biosimilar is highly similar to a reference medicine, with the same safety and efficacy in one therapeutic indication, safety and efficacy outcome data may be used for other indications approved for the reference medicine. This is known as extrapolation, and means that fewer clinical trials need to be carried out with the biosimilar. Extrapolation of data to other indications is always scientifically justified by evidence generated in advanced comparability studies (quality, non-clinical and clinical). Depending on the molecule, non-clinical analytics and research can deliver more precise information about the similarity than clinical trials. Also, when clinical trials are performed, they are done with a sensitive study population to allow extrapolation, including shared mechanisms of action.

#### FAQ 6: If a biosimilar is approved for another condition, how do you know it will work for my condition?

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- Your biosimilar medicine has been approved based on evidence showing that the structure is the same as the reference biological medicine. This begins with characterization of the biosimilar molecule and careful analysis of how the biosimilar and the reference molecule compare [2].
- The next step is to confirm that the safety and efficacy are the same, in a confirmatory clinical trial in one or two of the same indications as the reference biological medicine. This confirms that the biosimilar acts in the same way as the reference product in humans.
- Adding together these two pieces of evidence confirms the 'similarity' of the reference biological medicine and the biosimilar, regardless of the indication.
- The next step is called 'extrapolation'. This gathers all the information available and creates a bridge between the results from the studies of the reference biological medicine and the studies of the biosimilar. This provides the manufacturer, the authorities and the doctors with the assurance that the reference biological medicine and the biosimilar are versions of the same molecule and will act the same way in all of the approved indications.
- Using infliximab and inflammatory bowel disease as an example: [3],[4]
  - The original version of infliximab has been approved for use in inflammatory bowel disease (IBD), psoriasis, ankylosing spondylitis and rheumatoid arthritis.
  - Extensive laboratory studies (analytical) were carried out to establish that the biosimilar version of infliximab is highly similar to the infliximab reference product in all important features.

- Biosimilar infliximab was then confirmed as highly similar to the reference product in both ankylosing spondylitis and rheumatoid arthritis, by means of clinical studies. This added to the evidence of the similarity between the reference biologic medicine and the biosimilar.
- The combination of the laboratory evidence and the clinical data was used to confirm that the infliximab reference product and its biosimilars were versions of the same molecule.
- This means that the indications applicable to the reference biological medicine could be extrapolated to the biosimilar version. In this case, this means that both versions will also be effective in the treatment of IBD and psoriasis.

## 2.4 MOVING BETWEEN REFERENCE BIOLOGICAL MEDICINES AND BIOSIMILARS: SWITCHING AND SUBSTITUTION

Once a biosimilar is approved in Europe, it can be prescribed to patients. The option of changing from a reference product to a biosimilar is performed by the clinical decision-maker and can vary between countries and regions according to national and local policies.

- **Interchangeability** is a medical term in the EU, and describes the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another. In Europe the European Medicines Agency confirms that safety and efficacy are the same between the biosimilar and the reference product. However, the policy on interchangeability is set by the national authorities.
- Replacement may be by:
  - **Switching**, which is when the authorised prescriber, usually the doctor, decides to exchange one medicine for another medicine with the same therapeutic intent.
  - **Substitution** (automatic), which is the practice of handing out (dispensing) one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the authorised prescriber. Substitution of biological medicines is not applied in most EU Member States.

See table A3 in the annex for examples of national policies regarding the introduction and substitution of biosimilars and reference biological medicines.

For a nurse, it is important to understand that there is no such thing as a 'one size fits all' approach for the use of biosimilars. Different countries have their own policies and regulations, and this can vary between regions and even between hospitals and institutes. Nurses and other healthcare professionals must be familiar with, and follow, the policies in their country, region or hospital, and use these to guide the process and communicate with healthcare professionals and patients.

## 2.5 REAL WORLD DATA ON BIOSIMILAR MEDICINES

The quality, safety and efficacy of biosimilar medicines are assessed and tested with comparability studies (including clinical trials) before the medicine is approved, but these evaluations do not consider cost-effectiveness.

To understand the effect of a medicine in everyday use, including how the full range of real patients use the medicine and what its cost-effectiveness is, researchers may carry out real-world studies,

usually after approval, to collect real-world data. This is analysed to create real-world evidence, which corresponds with practical, everyday use rather than predicted, expected or forecasted outcomes. Real-world evidence can be used to support communications with patients and colleagues. Patients may be monitored for long periods of time in a real-world setting to collect real world data. So far, there are more than 10 years of real-world experience in the use of biosimilar medicines.

## 2.6 REFERENCES

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## 3 THE BENEFITS OF BIOSIMILARS

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By bringing competition and prescriber and patient choice, biosimilars, can be more cost-effective than the reference biological medicine while offering the same therapeutic value in terms of safety and efficacy. This could save money on the healthcare budget, ensuring long term sustainability. It also could mean that health systems can treat more patients as the access thresholds may be lowered, allowing inclusion of patients who could not previously have been treated. It could also reduce under-treatment, and allow healthcare systems to offer additional forms of support or care. This may also be true of switching patients to another biosimilar or to reference biological medicines, as tender agreements and manufacturers' discounts can mean that the original form of the medicine is more cost-effective.

### 3.1 IMPROVING ACCESS

#### 3.1.1 What's in it for us? Benefit sharing following the introduction of biosimilar medicines

Introducing biosimilar medicines may not always lead to immediate savings. Where savings are achieved, this may not mean benefit for the unit or team in charge of the biosimilar medicines introduction, but may feed directly into local, regional or even national healthcare budgets. Although this still benefits patients and healthcare systems, it can make the benefits seem less tangible for individual teams. A simple example is that more affordable biosimilars can lead to an increase of patients treated with this molecule. The investment might be the same, but the general health outcome can be better because more patients can benefit from the biological treatment approach.

'Benefit sharing' or 'gain sharing' schemes are collaborative processes set up between the stakeholders – the healthcare commissioners and providers – that support the use of affordable medicines. These can lead to greater efficiencies in the use of medicines, and mean that the cost savings are distributed to the healthcare teams and groups involved. Benefit sharing therefore provides motivation to make the most efficient use of medicines, and means that the savings can go into patient care, such as healthcare products and services [1, 2].

In practice, benefit sharing agreements can mean that all stakeholders involved gain benefits from switching between reference biological medicines and biosimilars, or vice versa:

- More patients can be treated thanks to increased treatment cost-effectiveness.
- The savings generated can be used to increase nursing staff, which is needed as more patients are being treated.
- Increased nursing staff means that patients will receive better care, contributing to improved health outcomes.
- The savings are available for the healthcare budget or the treatment of other patients and other diseases.

#### **Case studies 1: The benefits of switching from the infliximab reference product to biosimilar infliximab in patients with inflammatory bowel disease**

After running a hospital tender for infliximab (biosimilar and reference biological medicine) at the AZ Delta hospital, Roeselare, Belgium, a decision was made to perform a mandatory switch for inflammatory bowel disease (IBD) patients, moving all patients from a reference biological medicine to a biosimilar. The key to the changeover was information and education.

The important first step was to inform the patients, and so the team sent all patients a personal letter and also explained it to them face-to-face. The focus was on the advantages for the patients.

The IBD team felt it was crucial to work with and inform all the other caregivers involved in the switch process. At AZ Delta, this included the pharmacists, day clinic nurses, physicians and inpatient nurses. The consultant IBD nurse played a central role in this interdisciplinary journey.

The team wrote personal letters to the patients' general practitioners, as patients may raise questions and concerns after the product exchange. There was also an interdisciplinary lecture for all stakeholders based on some of the questions that patients were likely to ask:

- What is a biosimilar?
- What is the difference between a biosimilar and the reference biological medicine?
- Are biosimilar medicines equally effective?
- Can effectiveness be lost after the exchange between the reference biological medicine and the biosimilar?

The team also created a pocket dictionary for the nurses that included frequently asked questions.

The conclusion is that it is important to communicate with patients before, during and after the switch. Comparing patients' results from before and after the switch was helpful.

While the switch to the biosimilar biological medicine was mandatory, the team found a number of positive outcomes:

- Benefits to the nurses (and the patients):
  - The process allowed the team to re-examine the administration procedure to make it simpler. This resulted in shorter waiting times, harmonising procedures, improving pre-delivery procedures, etc.
- Benefits to the patients
  - Thanks to the savings, the hospital was able to increase from one part-time to one full-time IBD nurse to support patients during their clinic visits.
  - The team could provide support to help with problems or questions at home.
  - The team improved the organisation of the care pathway.
- Benefits to the hospital and the healthcare system:
  - The biosimilar was less expensive than the original biological medicine so, by using the biosimilars, the team could make more biological medicines available to more people.
  - The team could maintain the financial viability of the healthcare system for longer.

### 3.1.2 Improving access to biological medicines

Biological medicines have transformed healthcare and the handling of certain diseases, drastically improving patient care. Most of them have become the standard of care for some therapy areas. However, biological medicines may be higher cost than new or existing small molecule drugs because of their complexity, meaning that research, development and manufacturing costs can be considerably higher. This leaves governments with a conundrum: effective medicines are available, but their access can be limited because of high prices, particularly when pharmaceutical budgets are being reduced and demands on healthcare are increasing.

Biosimilar medicines can bring cost savings for healthcare systems, and could therefore increase patient access in certain regions or countries thanks to greater cost-effectiveness and the increase in competition in the biologics market.

Case studies 2: Cost savings from implementing biosimilar medicines
<ul style="list-style-type: none"> <li>• In the UK, York Teaching Hospital Foundation Trust switched from the reference infliximab biological medicine to biosimilar infliximab in September 2015, and saved around £450,000 (approximately €516,600) in the first year. The role of the IBD nurses, both in informing and supporting patients, and in working with the staff in the day unit where the infusions were administered, was central [2].</li> <li>• In a Danish study, researchers were looking at a switch to a biosimilar product in patients with rheumatoid arthritis, ankylosing spondylitis or spondyloarthritis, and estimated that the annual savings were between around DKK8,900 and DKK64,600 (about €1,195 to €8,675) per patient, depending on the type of administration. The process of switching itself was not cost-intensive. The study concluded that, in this case, "the cost of implementing switching [was] very limited and savings incurred by the significantly lower prices of biosimilar compared to originator [made] the switch instantly economically viable" [3, 4].</li> </ul>

With the introduction of biosimilar medicines, many payers and health authorities have decided to change their treatment guidelines to allow earlier initiation of biologic therapy or to provide prescribers and patients with more treatment options.

Case studies 3: How changing guidelines can affect biosimilar use
<ul style="list-style-type: none"> <li>• In Sweden, before biosimilar filgrastim was launched, Neupogen® (filgrastim from Amgen) could only be administered to patients after the consent of three physicians. Because of the reduction of the treatment costs due to biosimilar competition, the authorities relaxed the restrictions on prescribing, requiring consent from only one physician. This resulted in a 500% increased use of biosimilar filgrastim.</li> <li>• In the UK, NICE updated its treatment guideline with the introduction of biosimilar infliximab now also allowing adult patients with non-radiographic axial spondyloarthritis to be treated. This indication was restricted for Remicade® (infliximab from Janssen Biotech) due to its high cost. After the launch of the biosimilar erythropoietin, NICE assessed the treatment as also cost-effective for cancer patients with treatment-induced anaemia.</li> </ul>

### 3.1.3 Expanding healthcare teams

Where the savings are fed back into the department, hospitals may be able to expand their teams, offering more support from colleagues or access to more hours for specialist nurses, and better training and support for non-specialist healthcare professionals.

Case studies 4: Where benefit-share means extra nurses
<ul style="list-style-type: none"> <li>• In the UK, a benefit share agreement following an infliximab switch allowed York Teaching Hospital Foundation Trust to employ an IBD specialist nurse in Scarborough. The savings were</li> </ul>

used as the argument to create the new role, and mean that patients did not have to travel so far.

- At the Royal Free London Foundation Trust in the UK, a benefit share agreement and savings of £2.5 million (around €2.9 million) with the use of biosimilar medicines in gastroenterology has allowed the recruitment of a couple of new IBD nurses. While the time of the agreement is limited, the additional support provided by the nurses will hopefully allow their roles to be extended [2].

### 3.1.4 Improving access to healthcare

Access to biological medicines can be restricted for patients because of the pricing and reimbursement procedures of the individual government and healthcare system. The introduction of competition from biosimilar medicines provides an opportunity for governments throughout Europe to increase patient access to treatment, while at the same time supporting the sustainability of healthcare budgets.

Generic medicines (off-patent versions of small molecule medicines) can significantly decrease inequalities in healthcare [5, 6] and the introduction of biosimilars had led to an increase in patient access to biological medicines [7].

## 3.2 REFERENCES

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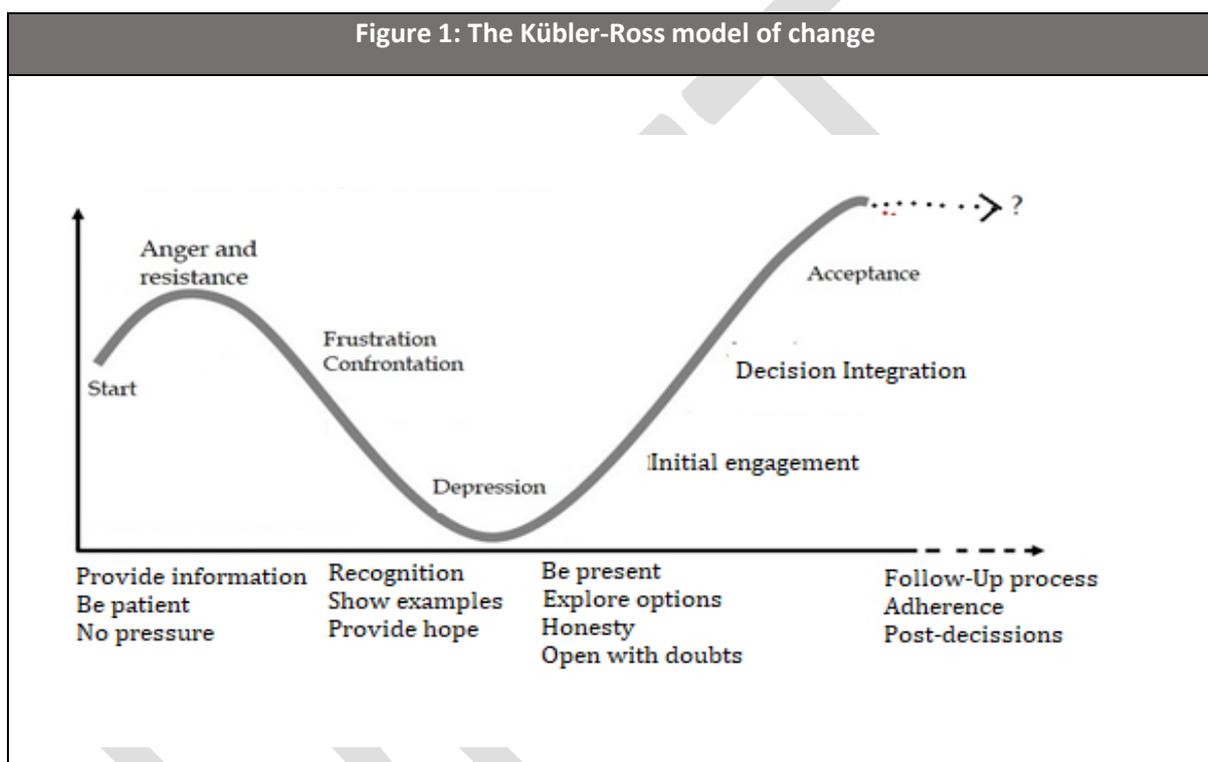
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## 4 SWITCHING TO A BIOSIMILAR

### 4.1 THE THEORY OF CHANGE MANAGEMENT

Nurses know from experience that changing medication can be challenging for patients who may already be struggling to come to terms with diagnosis and treatment. The process of change involves a journey from doubt, worry and even anger to understanding and acceptance.

In nursing, there are a number of theories and practices around change management, for example the Kübler-Ross model of change (figure 1). This can be used to describe people's feelings and emotions during this process of change.



Source: NVZA

The Kübler-Ross model reflects how nurses deal with patients in many different situations, not just with the introduction of biosimilar medicines. These include diagnosis, treatment initiation or change, and lifestyle change.

### 4.2 MANAGING THE EXCHANGE BETWEEN REFERENCE BIOLOGICAL MEDICINES AND BIOSIMILARS

Nurses play a crucial role [1] in communicating with patients and providing support and reassurance, before, during and particularly after the switch between the types of biological medicines. This builds on their many years of education and nursing experience with patients in different situations. It is a process that requires time, patience and care.

The nurse's role in building patients' confidence and commitment to the switch, following the theory shown in the Kübler-Ross model, can be summarised in eight steps [2]:

<b>Table 2: Supporting biological product exchange through communication: Eight steps</b>		
<b>Steps in building patient confidence and commitment</b>	<b>Role of the nurse</b>	<b>Patient's response</b>
<b>Step one: Contact</b>	Provide clear information, begin to create awareness ahead of the introduction of the biosimilar medicine.	"I've heard about it"
<b>Step two: Awareness</b>	Build on the information provided.	"I'm aware of it and I need to know more"
<b>Step three: Understanding</b>	Show examples, answer questions and deal with challenges as patients begin to understand how the change will affect them.	"I understand it and what it will mean for me"
<b>Step four: Positive perception</b>	Reinforce the positive benefits of the change, including to the patient and the care that they will receive.	"I support it"
<b>Step five: Experimentation</b>	Talk patients through the processes of administration, particularly if there are any changes; let them see the new medicines and the information that will come with them; provide any new skills that they may need.  Deal with any additional questions.	"I will try it out"
<b>Step six: Adoption</b>	Begin treatment with the biosimilar medicine, and answer questions as they arise.  Continue to confirm that the biosimilar medicine is still the same treatment.	"I want it to happen"
<b>Step seven: Institutionalisation</b>	Reinforce the previous steps, as the treatment begins to become 'normal'.  Follow-up any questions previously asked, and deal with new post-switch questions.	"It's how we do things"
<b>Step eight: Internalisation</b>	Emphasise and reiterate the information already passed on.  Continue to reassure patients as they have treatments, and counter any negative thoughts to avoid the nocebo effect (the worsening of symptoms induced by the switch to another active therapy) [3].  Continue to deal with questions as they arise.	"It's ours"

	<p>Monitor adherence and compliance as the treatment with the biosimilar becomes routine.</p> <p>Link up patients who have fully accepted the change with patients who are still unsure.</p>	
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Source: Adapted from Conner [2]

### 4.3 INTRODUCING THE SWITCH

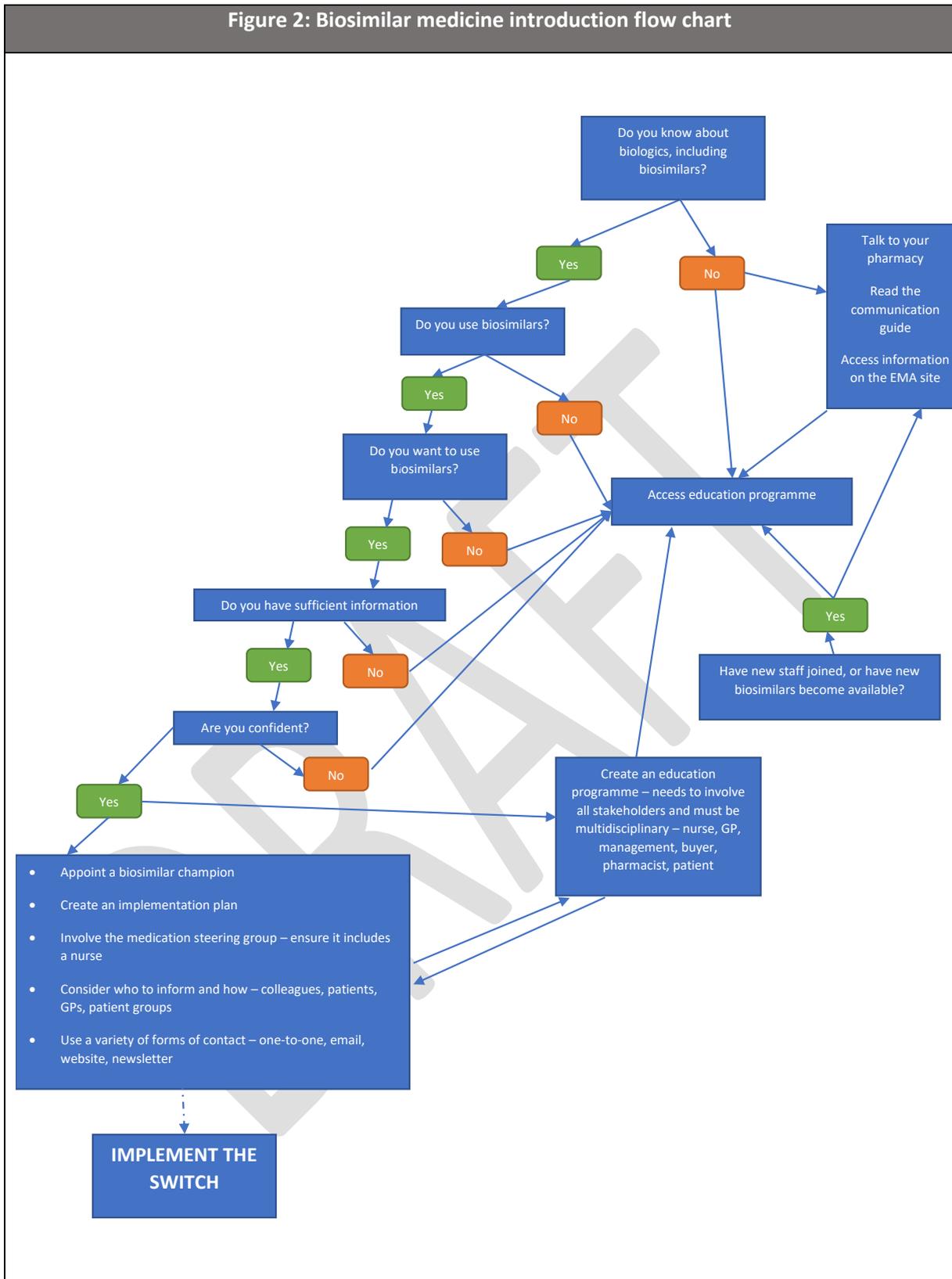
Communication plays a key role in introducing biosimilars to patients [4, 5]. When nurses discuss biosimilar switching with patients, and provide support throughout the process, it is important to keep in mind the benefits that biosimilars provide, for the patients, for the healthcare teams including nurses, and for the healthcare system as a whole. This means that it is essential, before the switch, that nurses and all members of the healthcare team know enough about biosimilars and have confidence in the role that biosimilars and similar biological medicines play in treating patients.

The flow chart in figure 2 shows the steps to ensure that the members of the multidisciplinary team are fully informed and prepared for the implementation of switching.

#### FAQ 7: Can the biosimilar have a different packaging or delivery system?

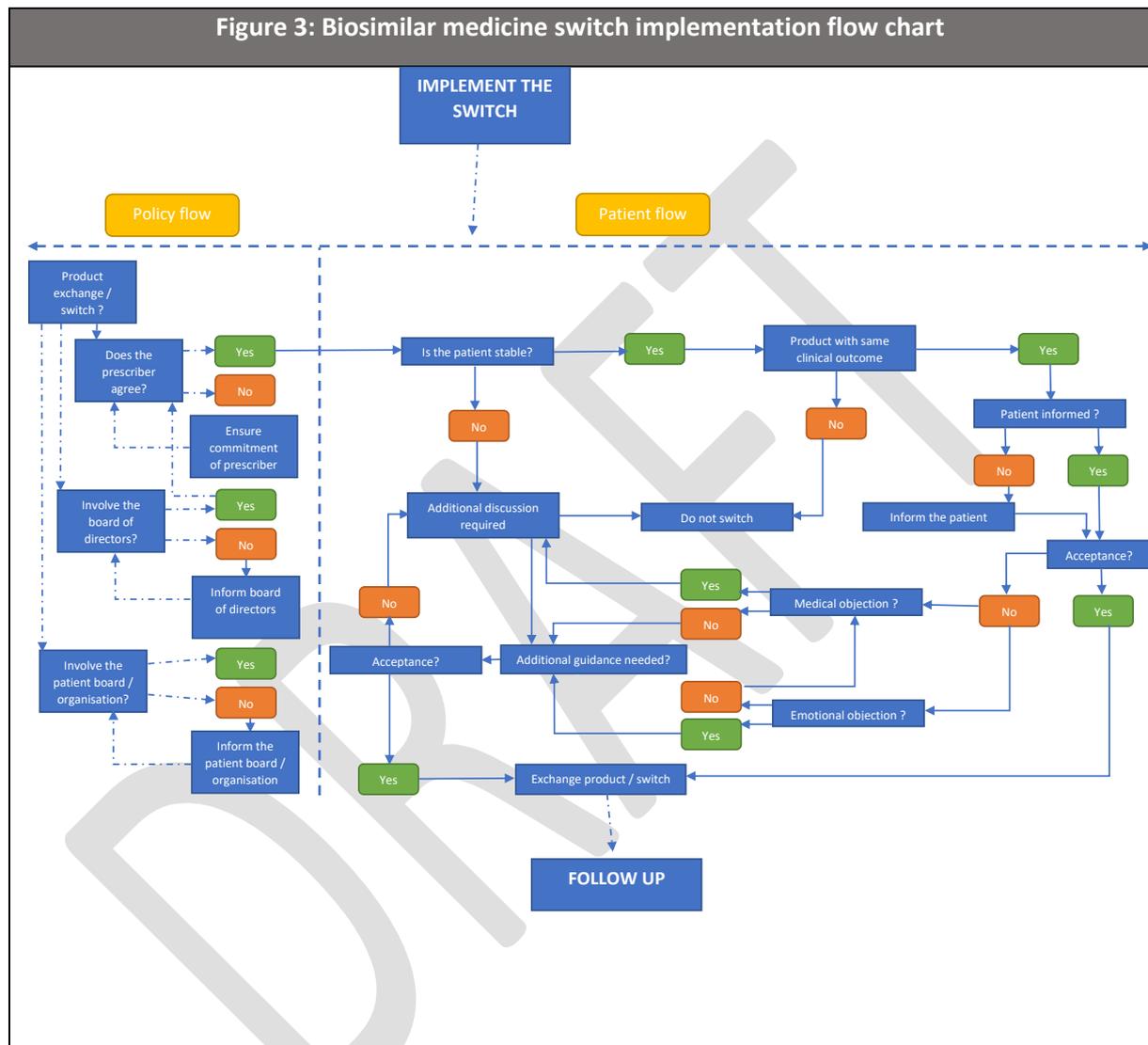
- Yes, the physical appearance of the product might be different as patents can also apply on the applicator of the medicine. This however does not influence the safety and efficacy of the biosimilar.
- The dose and route of administration of the biosimilar must be the same as those of the reference medicinal product.

Figure 2: Biosimilar medicine introduction flow chart



Once the decision for the switch is made, whether from reference product to biosimilar (or vice versa) or between biosimilars, and the implementation plan is in place, the next step is to implement the switch (see figure 3).

Patients may be concerned about changes in biological medicines, and will have a lot of questions. Positive language is important in answering questions, to provide confidence and reassurance. Patients need to know that their healthcare professionals understand the reasoning behind the change and are confident that it is the right thing to do. To avoid confusion, the team of nurses and other healthcare professionals should have a consistent explanation that is used by all.



Source: Based on a flow chart from NVZA [6]

Communication with patients throughout the process is vital. This can be through face-to-face meetings, phone calls, email, mHealth and comparable technologies, and social media such as WhatsApp® and Messenger®. This support should also address the issue of adherence and compliance, pharmacovigilance, adverse events, and product complaints. With these new technologies it is important to ensure that processes are in place to handle adverse events and product complaints in a timely and efficient matter. On an on-going basis, the support should allow patients the opportunity to discuss any issues and concerns with doctors, nurses and pharmacists.

Nurses are well-placed to understand the patient's perspective, for example the reluctance of a patient who has been stable on medication for some time, or who has finally found a medicine that suits after many changes because of lack of efficacy or unpleasant side effects.

#### FAQ 8: I am stable on this medicine and I don't want to change

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- The biological medicine that you are going to receive is just as safe and effective as the original medicine and fulfils the same quality requirements. It has been studied thoroughly and approved by the European Medicines Agency.
- The right time to switch may be when you are stable, as it means you are responding well to the molecule and don't need to switch to a different biological medicine.
- We will support you through the change and monitor your disease before and after, so that you, and we, are happy that nothing has changed.

#### FAQ 9: Might I have to change medicine again?

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- As more companies produce biosimilar forms of biological medicines, and competition in the market increases, there may be another biosimilar in the future that we could potentially switch you to.
- If we do make a change to another biosimilar medicine, we will carefully monitor you to make sure that it is still as safe and as effective for you.
- Other companies may also produce biosimilars that are easier to dose or administer, because they are delivered in different ways, or use different devices such as a better syringe. This could make your treatment faster or simpler.

#### FAQ 10: I'm not going to change!

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- In some regions, nurses will have to be understanding with patients and explain that the change may happen, and support them through it.
- In others, there may be a possibility of allowing individual patients to remain on the reference biological medicine.
  - Keeping discussions going is important because, as patients learn more about biosimilar medicines and increase their understanding and trust, they may be more open to change.
  - This is particularly important for patients who have had to change medications a lot to find the one that works best for them, and have finally become stable. This process may have damaged their trust in the process (see also 'FAQ: I am stable on this medicine and I don't want to change')

### FAQ 11: Might the medicine lose its effect after the change?

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- We will monitor your disease before and after you switch between biological medicines, and keep a close eye on you during the process.
- If you are worried about the switch, this may make your symptoms or side effects appear worse, so it feels as if the medicine isn't having as much of an effect. This is what we call the nocebo effect: it means that your trust and belief are important for good efficacy [3].
- Yes, effectiveness can be lost after switching from a reference biological medicine to a biosimilar. However, this isn't because of the switch. Your body can create antibodies to biological medicines, and this can happen with the reference medicine, or with a biosimilar.

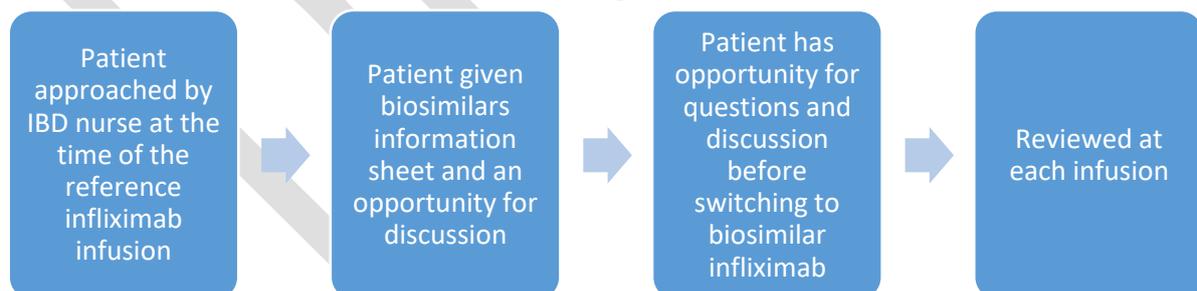
### FAQ 12: Why are you doing more tests, and why is my treatment taking longer?

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- We will measure the amount of medicine in your blood just before we administer the biosimilar, so that we can make sure we are giving you the right dose. This also means that we can keep a closer eye on you during the process.
- Sometimes when you are switched to biosimilars, the pharmaceutical company advises that the medicine should be treated as if it is a completely new one, which might mean that treatment will take longer.

### Case studies 5: Biosimilar infliximab in inflammatory bowel disease: Outcomes of a managed switching programme

The Southampton General Hospital, UK, developed the following managed switching programme with support from the local inflammatory bowel disease (IBD) patient panel, gastroenterologists, pharmacists, and the IBD nursing team, in order to switch patients from the reference infliximab biological medicine to Hospira's Inflectra (biosimilar):



#### Working with the patients

The patient panel, a group of 8-10 patients, met with the IBD clinical team every 6-8 weeks to provide the patient's perspective for both the service and the research projects. While the patients were concerned about gaps in the evidence base around the use of biosimilars in IBD, and around switching, they were reassured by the increase in monitoring built into the managed switching and the risk management programme. The patients were keen to see savings invested in development of the IBD service, including dietetic support and specialist nurses.

**Working with the healthcare professionals**

The healthcare professionals discussed biosimilars at the gastroenterology departmental meeting, with a focus on the scientific information about biosimilars and ways to improve the IBD service. The physicians were universal in their support, based on the reassurance provided by the risk management plan, which included robust pharmacovigilance procedures and the prevention of interchangeability by brand prescribing only. The physicians also stated clearly that they would need further investment to be able to deliver the programme, as they didn't have sufficient capacity.

**Funding the project**

The programme was funded through a gain share agreement, between the University Hospital Southampton NHS Foundation Trust and local clinical commissioning groups, and any savings were shared. This included:

- *Funding the managed switching programme*
- *Investing in the nurse-led IBD biologics service*
- *Developing an inpatient IBD nursing service*

New posts included a IBD specialist nurse post, a 0.5 whole time equivalent (WTE) clerical post, a 0.2 WTE pharmacist and a 0.2 WTE dietitian.

**The outcomes**

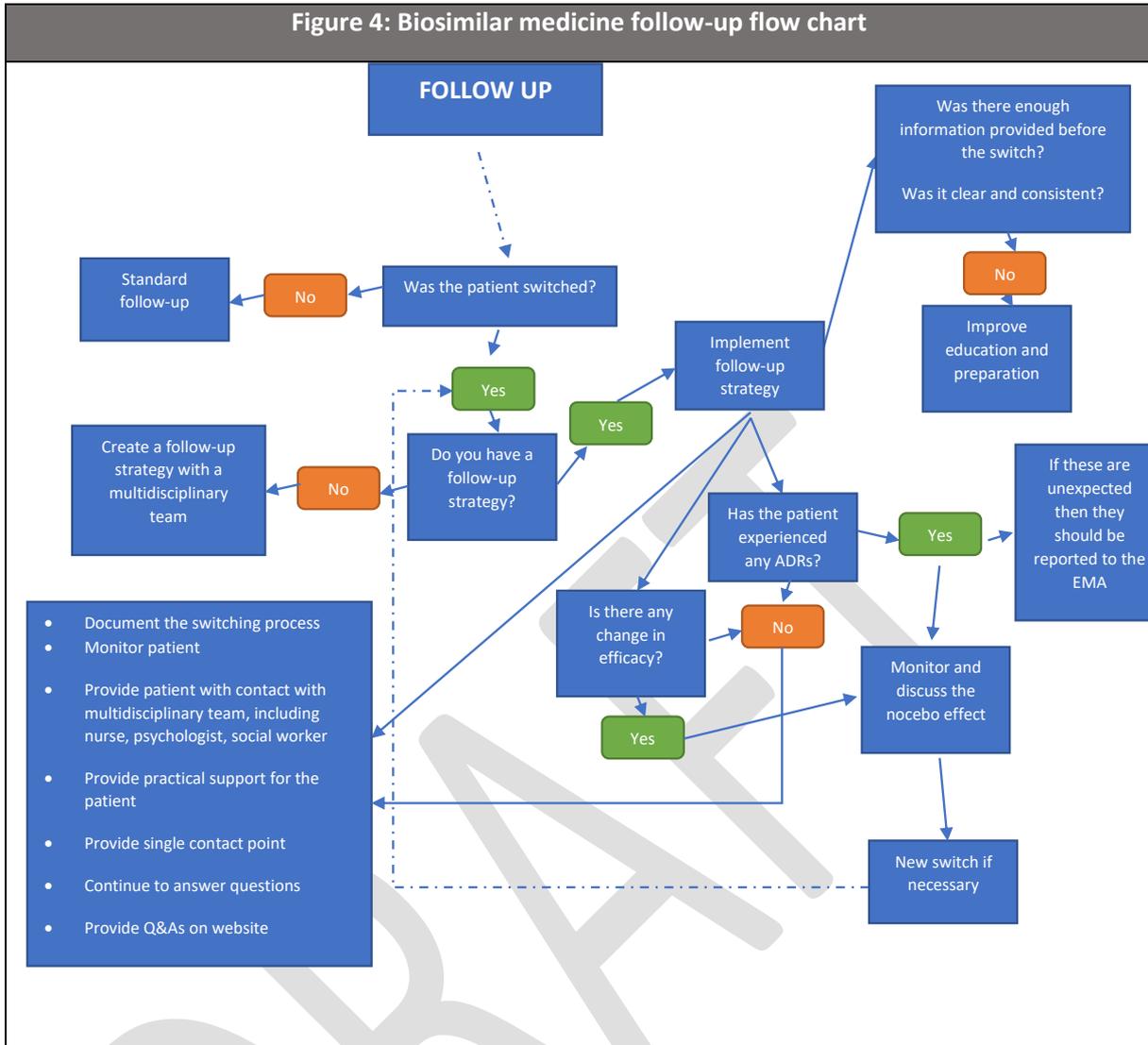
All of the infliximab-treated IBD patients who were looked after by the adult IBD service, were given the chance to take part. Those who agreed were switched to Inflectra at the same dose and frequency as the reference infliximab biologic medicine.

**4.4 AFTER CHANGING BIOLOGICAL MEDICINES: FOLLOW-UP AND SUPPORT**

Some patients can become very anxious during and after changes between biosimilar and reference biological medicines, and many questions will come after the switch. Support, reassurance, communication and information from nurses and other healthcare professionals are very important, particularly when patients have struggled to get a diagnosis and find an effective treatment in the past. This can be an emotional process for the patient and needs time and patience.

Nurses need to be available to answer questions once patients have changed their treatment, and knowing that they can have their questions answered will make patients feel more confident and comfortable. Figure 4 shows a flow chart looking at the follow-up strategy following a switch.

Figure 4: Biosimilar medicine follow-up flow chart



Some patients may worry that they feel worse on the biosimilar. This is likely to be a psychological effect because they are afraid of becoming ill again, and may be focussing on symptoms that they didn't notice before, or they misinterpret normal disease progression as side effects. This is known as the nocebo effect, which is when negative thoughts make it more likely that an intervention, such as changing to a biosimilar, will have a negative effect [3].

There have been a number of studies looking at adverse events after changing from reference biological medicines and biosimilars, and these show no differences in the rates or severity [7]. In a study carried out in Denmark looking at treatment failures when switching between reference etanercept (Enbrel) and the etanercept biosimilar Benepali, patients believed that it was 'obvious' that adverse events and loss of efficacy were a result of the switch to the biosimilar. Explaining that the reference and the biosimilar are the same treatment was effective in about 90% of cases [4, 8].

In another Danish study, researchers who were looking at a switch to a biosimilar product in patients with rheumatoid arthritis, ankylosing spondylitis or spondyloarthritis, concluded that communication strategies were an important part of the process [4, 5].

Educating patients about the normal course of their disease is particularly important to avoid the nocebo effect [3].

**FAQ 13: What if you accidentally give me the reference biological medicine or a different biosimilar after you have switched me to the biosimilar?**

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- The EMA's regulatory approval indicates that all biological medicines (both reference products and biosimilars) are safe, effective and of high quality.
- As for all medicines, we will monitor any potential side effects .
- We will make sure that there is a system in place to prevent any accidental switching.
- To minimise risk, all biosimilar medicines are prescribed by brand name, and their safety monitored through pharmacovigilance systems, under the supervision of the health authorities
- However, if this does happen, we will monitor you after the switch, as we would if you had been intentionally switched.

#### 4.5 PHARMACOVIGILANCE

An important requirement for the safety monitoring of all biological medicines is the need for product and batch traceability during daily use and at all levels in the supply chain. This covers the time from release by the manufacturer of the biological medicine and progress through the entire distribution chain, right through until the medicine is administered to the patient.

As required by EU law, every medicine will have a tradename or brand name together with the name of the active ingredient (described as the generic name, the common substance name, or the international non-proprietary name [INN]). To ensure traceability in the EU, medicines have to be clearly identified by the tradename and batch number; this is particularly important where there is more than one version of the biologic medicine. This process ensures that the medicine can be correctly identified if any product-specific concern arises [7].

Healthcare professionals, including nurses, play a vital role in collecting and reporting adverse medicine reactions for biological medicines, including biosimilars. They need to record the name of the product (brand name) and the batch number or code, along with a suspected adverse reaction, and report this using the online or web-based reporting tool used in their region.

It is important that healthcare professionals report any suspected adverse drug reactions (ADRs) of a reference biological medicine or biosimilar even if the reaction is already listed in the reference medicine's SmPC and the patient leaflet. Healthcare professionals also play an important role in explaining to patients their responsibility for reporting any adverse drug reactions, including how they should make reports and why the reports are important.

**FAQ 14: What should I do if I think the biosimilar is causing side effects?**

\*sample answer – answer may differ by country, region, hospital or a range of other factors.

- If you think any medicine is causing side effects, especially if they are ones you haven't seen before, or if you are not expecting them, you should tell a healthcare professional.
- You can also report side effects through the patient reporting system provided by your country's [national authority](#).
- All versions of biological medicines, including the reference biological medicine and the biosimilar versions, are expected to show similar patterns of side effects.

- There have been no reports of safety issues specifically related to biosimilars [9].

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## 5 CLOSING REMARKS AND RECOMMENDATIONS

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### 5.1 CLOSING REMARKS

We hope that this information guide is of use to you. Although we have more than ten years of biosimilars experience, the field of biosimilars is, for some, a still new and evolving one. If you need more information, please see the [European Medicines Agency \(EMA\) website](#).

Please get in touch (see section 6.5) if you hear questions from your patients that are not covered, or if you have any responses or case studies that you think may help other healthcare professionals, and the team will look at including them in future versions.

### 5.2 RECOMMENDATIONS

Introducing biosimilars and moving patients between biosimilars and the reference medicines can be of benefit to patients, healthcare teams and the healthcare system as a whole, but it has to be handled with care.

Nurse-led programmes can ensure the continuity of information and education before, during and after the change of medication. Working together in interdisciplinary teams and ensuring clear and consistent communication and information at all levels, from management to patients, can result in gains in care quality and costs [1].

### 5.3 REFERENCES

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## 6 ANNEX

### 6.1 GLOSSARY

<b><i>Benefit share</i></b>	Collaborative processes set up between the stakeholders – the healthcare commissioners and providers – that support the use of less expensive medicines, where cost savings are distributed to the healthcare teams and groups involved. Also known as gain share
<b><i>Biological medicine</i></b>	Biological medicines (including biosimilar medicines) are produced from living organisms, such as mammalian cells, bacteria or yeasts. Biological medicines are usually larger and more complex than chemically-synthesised compounds
<b><i>Biosimilar</i></b>	A medicine highly similar to a marketed biological medicine (reference medicine or reference product)
<b><i>European Medicines Agency (EMA)</i></b>	The European regulatory agency responsible for approving drugs for the market in Europe
<b><i>European public assessment reports (EPAR)</i></b>	Full scientific assessment reports of medicines approved for the market by the EMA
<b><i>Extrapolation of indications</i></b>	Approving a biosimilar for the same indications as the reference medicine. If a biosimilar is highly similar to a reference medicine, with the same safety and efficacy in one therapeutic indication, safety and efficacy outcomes data may be used for other indications approved for the reference medicine
<b><i>Interchangeability</i></b>	Interchangeability refers to the possibility of exchanging one medicine for another medicine that is expected to have the same clinical effect. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another (see also <b>switching</b> and <b>substitution</b> )
<b><i>International non-proprietary name (INN)</i></b>	The name of the active ingredient in a medicine. It is also described as the generic name or common substance name
<b><i>Nocebo</i></b>	The worsening of symptoms that may be seen when patients switch to another active therapy, such as a biosimilar
<b><i>Pharmacovigilance</i></b>	Monitoring, detecting and reporting adverse effects and other issues relating to medicines
<b><i>Real-world data</i></b>	Information collected on medicines in every-day use
<b><i>Real-world evidence</i></b>	Evidence created from analysis of real-world data
<b><i>Reference product or reference medicine</i></b>	The original version of a biologic medicine

<b>Substitution</b>	The practice of dispensing one medicine instead of another equivalent and interchangeable medicine at pharmacy level without consulting the authorised prescriber – this is an automatic process
<b>Switching</b>	When the authorised prescriber decides to exchange one medicine for another medicine with the same therapeutic intent

## 6.2 LIST OF BIOSIMILARS

Since the introduction of the first biosimilar into clinical use in 2006, an increasing number of biosimilars have been approved and safely used in the EU. A list of approved biosimilars in Europe can be found on the [EMA website](#). By 2017, EU approved biosimilar medicines had delivered over 700 million patient days of treatment [1].

<b>Table A1: Biosimilar medicines approved in Europe (last updated 30 March 2018)</b>			
<b>Active substance (year of first approval)</b>	<b>Brand name of reference product</b>	<b>Brand name of biosimilar</b>	<b>Therapeutic area</b>
Adalimumab (2017)	Humira	Amgevita, Cyltezo, Imraldi, Solymbic	Rheumatoid arthritis; Juvenile idiopathic arthritis; Axial spondyloarthritis; Psoriatic arthritis; Psoriasis; Hidradenitis suppurativa; Crohn's disease; Ulcerative colitis; Uveitis
Bevacizumab (2018)	Avastin	Mvasi	Breast Neoplasms; Carcinoma, Non-Small-Cell Lung; Carcinoma, Renal Cell; Fallopian Tube Neoplasms; Ovarian Neoplasms; Peritoneal Neoplasms
Enoxaparin sodium (2016)	Lovenox	Inhixa, Thorinane	Venous thromboembolism
Epoetin alfa (2007)	Epogen	Abseamed, Binocrit, Epoetin Alfa Hexal	Anaemia; Consequence of chronic kidney failure; Follow-up of cancer treatment
Epoetin zeta (2007)	Epogen	Retacrit, Silapo	Anaemia; Autologous blood transfusion; Consequence of chronic kidney failure; Follow-up of cancer treatment

Etanercept (2016)	Enbrel	Benepali, Erelzi	Rheumatoid arthritis; Psoriatic arthritis; Plaque psoriasis; Ankylosing spondylitis
Filgrastim (2008)	Neupogen	Accofil, Filgrastim Hexal, Grastofil, Nivestim, Ratiograstim, Tevagrastim, Zarzio	Neutropenia; Follow-up of cancer treatment; Hematopoietic stem cell transplantation
Follitropin alfa (2013)	Gonal-F	Bemfola, Ovaleap	Anovulation (disturbance in menstrual cycle)
Infliximab (2013)	Remicade	Flixabi, Inflectra, Remsima	Rheumatoid arthritis; Crohn's disease; Ulcerative colitis; Psoriasis; Psoriatic arthritis; Ankylosing spondylitis
Insulin glargine (2014)	Lantus	Absaglar, LUSDUNA	Diabetes mellitus
Insulin lispro (2017)	Humalog	Insulin lispro Sanofi	Diabetes mellitus
Rituximab (2017)	Rituxan	Blitzima, Truxima, Rixathon, Riximyo, Ritemvia, Rituzena	Rheumatoid arthritis; Chronic lymphocytic leukaemia; Non-Hodgkin's lymphoma; Microscopic polyangiitis; Wegener granulomatosis
Somatropin (2006)	Genotropin	Omnitrope	Pituitary dwarfism; Prader-Willi syndrome; Turner syndrome
Teriparatide (2017)	Forteo	Movymia, Terrosa	Osteoporosis
Trastuzumab (2017)	Herceptin	Ontruzant	Early and metastatic breast cancer; metastatic gastric cancer

**Table A2: Biosimilar medicines in development (last updated 8 December 2017)**

<b>Active substance</b>	<b>Therapeutic area</b>
Cetuximab	Colorectal cancer; Head and neck cancer
Insulin aspart	Diabetes mellitus
PEG-filgrastim	Neutropenia; Follow-up of cancer treatment; Hematopoietic stem cell transplantation
Ranibizumab	Macular degeneration
Eculizumab	Cancer
Darbepoetin alfa	Anaemia

Glatiramer acetate	Multiple sclerosis
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Source: Panesar [2]

### 6.3 ADDITIONAL SUPPORTING INFORMATION

#### Case studies A1: Real world data and clinical trials can help to support the safety and efficacy of biosimilar medicines

- Omnitrope, a biosimilar of Genotropin (somatropin) was well tolerated and effective in the treatment of a wide range of paediatric conditions in PATRO Children, an ongoing observational, longitudinal, non-interventional, global post-marketing surveillance study in children requiring growth hormone treatment [3].
- Data from the DANBIO registry from 802 patients with inflammatory arthritis switching from Remicade (infliximab) to the biosimilar Remsima showed no negative impact on disease activity [4].
- In two real world studies of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (SpA) or ankylosing spondylitis (AS) carried out by Biogen, disease activity was largely unaffected in RA, PsA and SpA, and the rate of discontinuations was low in RA, PsA or AS [5].
- In the NOR-SWITCH Phase 4 study, there was no inferiority in outcomes for patients switching from the reference infliximab to the biosimilar infliximab, compared with the patients who stayed on the reference biologic medicine [6, 7].

#### Table A3: Examples of national policies on the introduction and substitution of biosimilars and reference biological medicines

- Austrian Medicines and Medical Devices Agency
  - Prescribing biosimilars to treatment-naïve patients [or] an exchange of the biosimilar for an originator biological is appropriate, provided that this is done under supervision of the prescribing physician [8].
- Medicines Evaluation Board – MEB (The Netherlands):
  - Exchange between biological medicines (regardless of whether they are innovator products or biosimilar medicinal products) is permitted, but only if adequate clinical monitoring is performed and the patient is properly informed [9].
- Finnish Medicines Agency – Fimea (Finland):
  - Biosimilar medicines are interchangeable with their reference products under the supervision of a healthcare person [10].
- Paul Ehrlich Institute (Germany):
  - Biosimilars can be used in the same way as the reference products to which they have shown equivalence. This implicitly covers both patients who have not yet received biological therapy as well as patients who have previously received the reference biologic medicine [11].
  - Automatic substitution is not allowed in Germany and the central role of the physician is emphasized: “The Paul-Ehrlich-Institute holds the view that any treatment decision of the physician must be based on scientific data” [11].
- Norwegian Medicines Agency

- The position of the Norwegian Medicines Agency is that switching between reference products and biosimilars during ongoing treatment is safe. Switching is necessary to achieve competition between equally efficient drugs. Competition leads to price reductions that lessen the financial burden of expensive biological drugs in the healthcare system. The Norwegian Medicines Agency has proposed that the Pharmacy Act § 6-6, which is the basis for generic (automatic) substitution in pharmacies, should be altered, eventually permitting automatic substitution of new classes of medicinal products, e.g. biological drugs [12].
- UK Medicines and Healthcare products Regulatory Agency (MHRA) and National Health Service (NHS)
  - Many biological medicines are coming off patent and “biosimilars” are becoming available. These medicines are highly similar to other biological medicines already licensed for use but are typically much cheaper than the originator products. This competition provides the NHS with an opportunity to save hundreds of millions of pounds, whilst also increasing access to these important medicines. There is the potential to realise savings of at least £200-300 million per year by 2020/21 if the NHS embraces the use of best value biological medicines in a proactive, systematic, and safe way. Our aim is that at least 90% of new patients will be prescribed the best value biological medicine within 3 months of launch of a biosimilar medicine, and at least 80% of existing patients within 12 months, or sooner if possible. This guidance is designed to support the NHS to achieve this [13, 14].

There are further examples in Medicines for Europe's [memo](#) on 'Positioning Statements on Physician-led Switching for Biosimilar Medicines'.

## 6.4 CONTRIBUTORS

This document was developed by [Suzanne Elvidge](#) on behalf of ESNO. ESNO was created to provide an effective framework for communication and co-operation between the European specialist nurses organisations, and to promote and represent the interests of specialist nurses in Europe.

The ESNO advisory group involved in the development of this communication guide represented five of its member organisations: European Oncology Nursing Society (EONS); Foundation of European Nurses in Diabetes (FEND); European League Against Rheumatism (EULAR) – nurses' section; European Skin and Dermatology Nurses; and Inflammatory Bowel Diseases. This document has been created in close collaboration with Medicines for Europe, EFPIA and EuropaBio, with funding from Medicines for Europe and EFPIA.

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<b>Names of supporting organisations</b>	
<b>European nursing organisations</b>	
ACENDIO	Association for Common European Nursing Diagnoses, Interventions and Outcomes
EDTNA/ERCA	European Dialysis and Transplant Nurses Association / European Renal Care Association
EfCCNa	European federation of Critical Care Nursing associations
ENDA	European Nurse Directors Association
EONS	European Oncology Nursing Society
EORNA	European Operating Room Nurses Association
FEND	Foundation of European Nurses in Diabetes
IFNA	International Federation of Nurse Anesthetists
EAUN	European Association of Urology Nurses
ESGENA	European Society of Gastroenterology and Endoscopy Nurses and Associate
ERNA	European Respiratory Nurses Association
EULAR	European League Against Rheumatism / Nurses section
EuSEN	European Society for Emergency Nursing
EANN	European Association Neuroscience Nurses
ACOVENE	Royal College of Veterinary Surgeons
ESE	European Society of Endocrinology Nurses
ECCO	European Crohn's and Colitis Organisation
HNHCP	Haematology Nurses & Healthcare Professionals Group
<b>European professional health organisations</b>	
EHA	European Hematology Associations

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