EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Publication of Risk Management Plan (RMP) summaries:

Proposal for analysis of the experience of the 1-year pilot phase

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Outline

- Background on summaries of ‘Risk Management Plan’ and pilot phase
- Objectives of the analysis
- Proposal for obtaining feedback from patients (and also healthcare professionals)

What is a Risk Management Plan?

- Document required by regulators for all medicines authorised in EU
- Describes what is known and not known about the safety of a medicine and the measures to prevent or minimise the risks
- Long and complex document, written in technical language
- It is not made public

Why produce a Summary of the Risk Management Plan?

- A *'live'* document which summarises the risks of a medicine and the measures to minimise such risks *(Full RMP is not published)*

- Expected target audience:
  - Stakeholders and partners with professional interest
  - General public (e.g. a patient who wants more information on his/her medicine)

- Complementary to other information available on medicines:
  - product information (i.e. medicine's leaflet)
  - assessment report (which describes the evaluation by EMA of each medicine)

Publication of summaries

- Aim:
  - Increased transparency
  - Increased public access to relevant information on medicines, in line with the legislation:
    - Article 26 of Regulation (EC) 1235/2010
    - Article 106 of Directive 2010/84/EU

    EU Member States and the European Medicines Agency to make public RMP summaries for all medicines authorised in the EU.

- 1 year pilot phase started in March 2014
- Includes medicines authorised from March 2014
- Medicines authorised before March 2014 & summary updates: *not included in pilot phase*

Other information on risk management plans by regulatory authorities

Japan PMDA
RMP

1. 医薬品リスク管理計画の概要
1.1 安全性検討事項

重要な特定されたリスク
低血圧

重要な特定されたリスクとした理由：

1. 国際共同第Ⅲ相比較試験（慢性血栓塞栓性肺高血圧症患者を対象とした試験及び肺動脈性肺高血圧症患者を対象とした試験）の併合解析において、低血圧を伴う有害事象はプラセボ群 9 例（3.7%）と比較して、リオシグアト群 49 例（10.0%）と多く認めている。低血圧を伴う有害事象を発症したことによる死亡例は認めておらず、治療の継続中止に至った症例は 1 例のみである。2 例の低血圧を伴う重篤な有害事象を発症した症例を認めているが、その他は非重篤と判定されている。しかし、本事象に伴う副次的事象（転倒、意識消失など）が顕著する可能性も考えられるため特に注意が必要な事象であると考えられる。
2. 慢性血栓塞栓性肺高血圧症患者を対象とした国際共同第Ⅲ相比較試験において、低血圧の有害事象はプラセボ群 3 例（3.4%）と比較して、リオシグアト群 16 例（9.2%）と多く認めている。重症度はプラセボ群の 1 例を除き、軽度又は中等度と判定されているが、本事象に伴う副次的事象（転倒、意識消失など）の発現も考えられるため特に注意が必要な事象であると考えられる。
3. 本剤の薬理学的作用により血管拡張が生じ、その結果低血圧が生じると考えられる。
4. 薬物相互作用（以下の薬剤との併用により、顕著な低血圧に至る可能性がある）
   - 硝酸剤または一酸化窒素供与体は、細胞内の cGMP を増加させる。第 1 相試験の結果から、本剤とニトログリセリンに薬物力学的相互作用があることが明らかになり、顕著な低血圧に至ることが認められたため。
   - PDE5 阻害剤は細胞内の cGMP 濃度を増加させる。後期第 II 相試験の結果から、本剤とシルデナフィルを併用した被験者において併用投与を中止する例が多く認められた。投与中止した理由の多くは、低血圧であった。

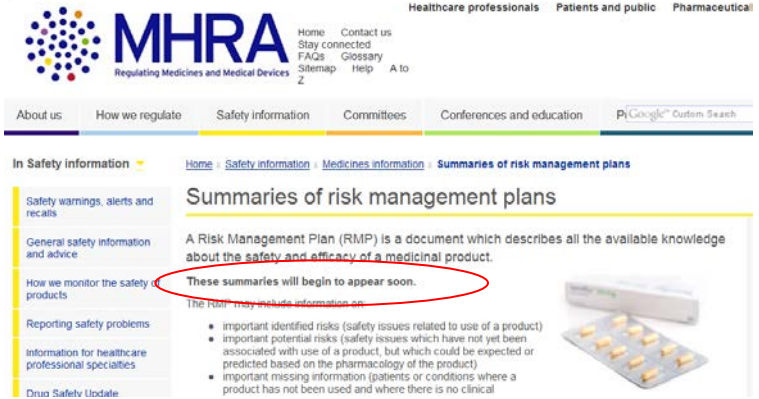
医薬品安全性監視活動の内容及びその選択理由：

【内容】

- 通常の医薬品安全性監視活動
- 追加の医薬品安全性監視活動として、以下を実施する。
  1. 市販直後調査

US FDA
Risk Evaluation and Mitigation Strategy (REMS)

MHRA (UK) announces publication of summaries of RMPs



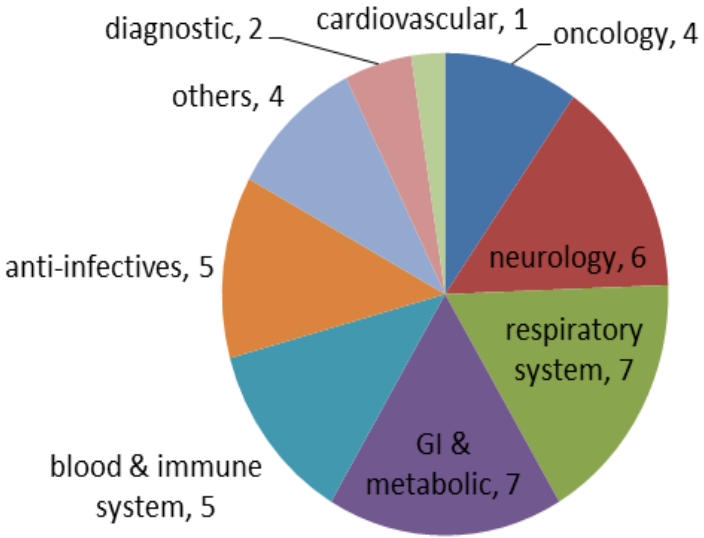
Current structure of Summaries of the Risk Management Plan

- Brief summary of the disease
- Summary of benefits
- Summary of main safety concerns:
  - Identified, potential and what is missing
- Summary of measures to minimise and prevent each safety concern
- Planned future and ongoing studies
- Major changes to the ‘Risk Management Plan’ over time

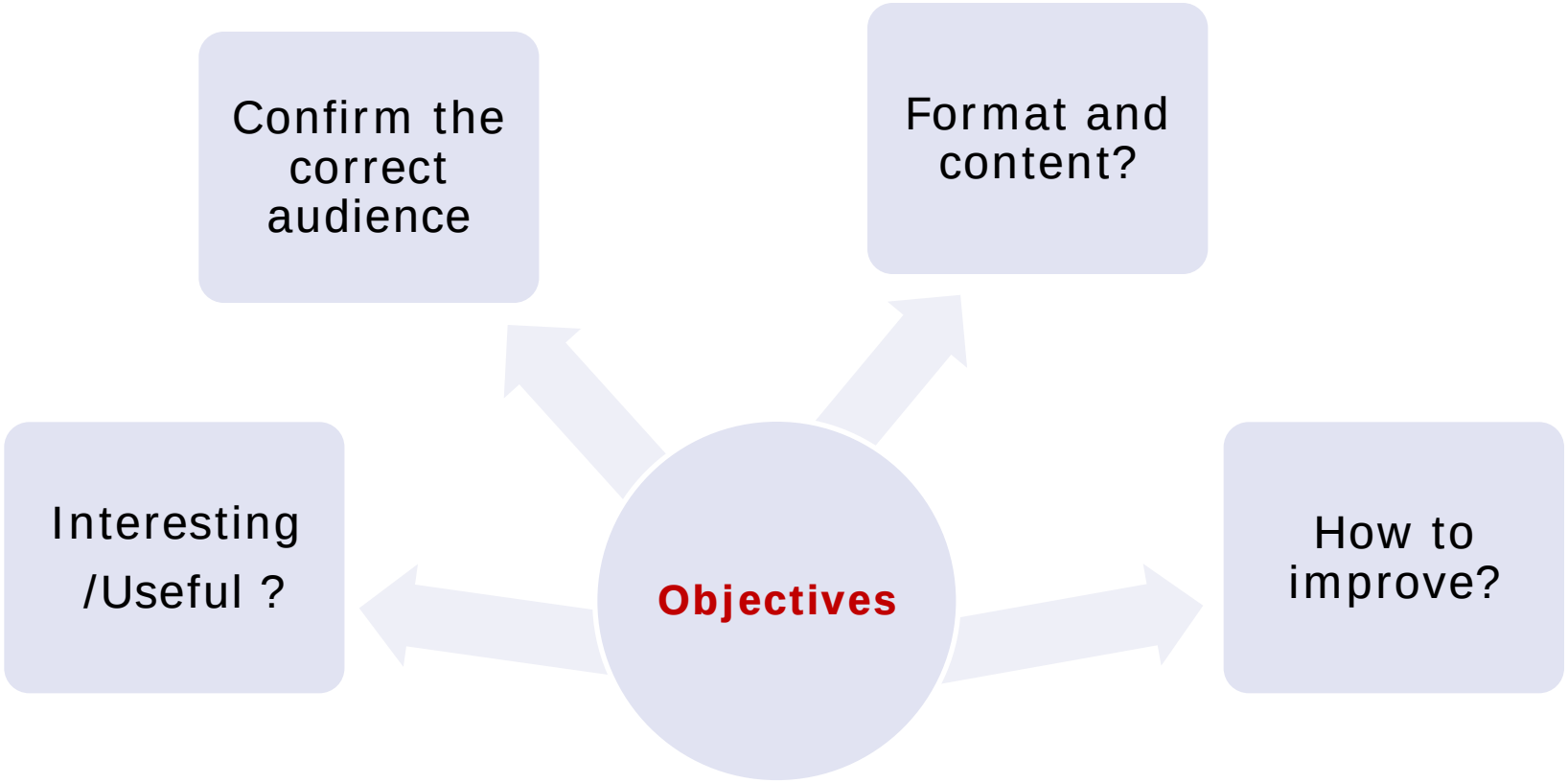
Current process for preparation of the summaries

41 summaries published so far

Summaries cover different therapeutic areas:



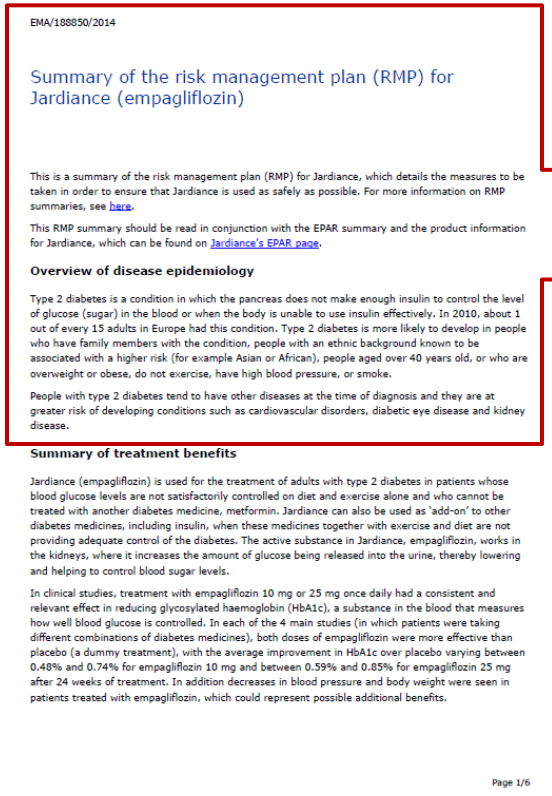
Objectives of the analysis



Feedback from patients (and healthcare professionals)

- Proposal to use a short questionnaire.
- Gather feedback on:
  - Interest and potential usefulness for patients
  - Explore opportunities for improvement
  - Other issues such as languages and potential contribution in the review
- Proposed to be sent to representatives/members of patients organisations but also to patients/members of the public not familiarised with the regulatory environment.

Example of a summary of a Risk Management Plan



EMA/188850/2014

Summary of the risk management plan (RMP) for Jardiance (empagliflozin)

This is a summary of the risk management plan (RMP) for Jardiance, which details the measures to be taken in order to ensure that Jardiance is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Jardiance, which can be found on Jardiance's EPAR page.

Overview of disease epidemiology

Type 2 diabetes is a condition in which the pancreas does not make enough insulin to control the level of glucose (sugar) in the blood or when the body is unable to use insulin effectively. In 2010, about 1 out of every 15 adults in Europe had this condition. Type 2 diabetes is more likely to develop in people who have family members with the condition, people with an ethnic background known to be associated with a higher risk (for example Asian or African), people aged over 40 years old, or who are overweight or obese, do not exercise, have high blood pressure, or smoke.

People with type 2 diabetes tend to have other diseases at the time of diagnosis and they are at greater risk of developing conditions such as cardiovascular disorders, diabetic eye disease and kidney disease.

Summary of treatment benefits

Jardiance (empagliflozin) is used for the treatment of adults with type 2 diabetes in patients whose blood glucose levels are not satisfactorily controlled on diet and exercise alone and who cannot be treated with another diabetes medicine, metformin. Jardiance can also be used as 'add-on' to other diabetes medicines, including insulin, when these medicines together with exercise and diet are not providing adequate control of the diabetes. The active substance in Jardiance, empagliflozin, works in the kidneys, where it increases the amount of glucose being released into the urine, thereby lowering and helping to control blood sugar levels.

In clinical studies, treatment with empagliflozin 10 mg or 25 mg once daily had a consistent and relevant effect in reducing glycosylated haemoglobin (HbA1c), a substance in the blood that measures how well blood glucose is controlled. In each of the 4 main studies (in which patients were taking different combinations of diabetes medicines), both doses of empagliflozin were more effective than placebo (a dummy treatment), with the average improvement in HbA1c over placebo varying between 0.48% and 0.74% for empagliflozin 10 mg and between 0.59% and 0.85% for empagliflozin 25 mg after 24 weeks of treatment. In addition decreases in blood pressure and body weight were seen in patients treated with empagliflozin, which could represent possible additional benefits.

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Unknowns relating to treatment benefits

It is not known if the effects of Jardiance on blood pressure and body weight reduction will, if sustained, provide a significant additional reduction in the risk of conditions such as heart attacks and strokes.

It is not known if children (aged between 10 and less than 18 years) with type 2 diabetes will have a similar treatment benefit profile as adult patients. Empagliflozin has also not been studied in patients taking a class of injectable diabetes medicines called glucagon-like peptide 1 (GLP-1) analogues.

Summary of Safety concerns: Important identified risks

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Urinary tract infection	Because empagliflozin increases the amount of sugar in the urine, it may encourage the growth of bacteria. Up to 1 patient in 10 treated with empagliflozin may experience a urinary tract infection, although in studies this also occurred in patients taking placebo. The risk is increased in patients with a history of urinary tract infections and infection may be more likely in women than in men.	Patients should drink plenty of water and other liquids, urinate often, and wipe themselves carefully after a bowel movement, particularly if they have previously had urinary tract infections. Serious infections may be caused by abnormalities in the urinary system, which could lead to permanent kidney damage. If patients have recurring infections, they should talk with their doctor who may consider additional tests. In addition, temporary interruption of empagliflozin may be considered in patients with complicated urinary tract infections.
Genital infection	Mild or moderate genital infection such as vulvovaginitis (inflammation of the vulva and vagina due to infection), moniliasis (a type of yeast infection), and balanitis (infection causing inflammation of the head of the penis) has occurred in up to about 1 patient in 20 given empaglifozin. Genital infection may be more likely in women than in men.	Preventive measures for genital infection are similar to those described above for urinary tract infections.
Fluid loss (volume depletion)	Because of the way empagliflozin works, which encourages urination, less than about 1 patient in 100 may experience symptoms related to fluid loss or dehydration (including low blood pressure and	Doctors should take extra care when prescribing Jardiance to patients in whom a drop in blood pressure due to fluid loss could pose a risk, such as patients with known cardiovascular disease, patients who have had low

Important identified risks

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Genital infection	Mild or moderate genital infection	Preventive measures for genital

Important potential risks

Risk	What is known
Cancer of the kidney and bladder (urinary tract)	An increased risk of renal cancer (cancer of the kidney) with empagliflozin was seen in one study in male mice, though not in other animals. In patients given empagliflozin, the overall number who developed cancer of the kidney or bladder was low and comparable to placebo. There is no obvious way that empagliflozin could increase the risk of renal tumours.
Kidney injury (renal impairment)	Because of the way empagliflozin works there is a risk of effects on the kidneys that could reduce their function (renal impairment). The overall number of patients with renal impairment was low. Renal impairment was slightly more common in patients receivin empagliflozin than in patients receiving placebo, and increa increasing age and use of diuretics (water tablets).
Liver injury	Liver injury was considered an important potential risk due changes observed in laboratory tests looking at liver functi The overall number of empagliflozin patients with liver inju been low and any relationship to empagliflozin treatment h been established.
Off-label use (e.g. for weight	Because empagliflozin produces weight loss (due to the inc sugar lost in the urine), there is the potential for inappropr

Summary of Safety concerns: Important potential risks

Important potential risks

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Summary of Safety concerns: Missing information

Missing information

Risk	What is known
Children (paediatric patients)	Empagliflozin has not been studied in patients younger than 18 years. A paediatric investigational plan (PIP) is in place to study the use of empagliflozin in paediatric patients aged 10 to less than 18 years.
Elderly patients	Since elderly patients are at increased risk of adverse events from medicines, post-marketing safety information will be collected regarding treatment of the elderly.
Pregnancy/breastfeeding	Empagliflozin has not been investigated in pregnant and/or breastfeeding women. Empagliflozin has not been shown to produce abnormalities during development in the womb. Experimental studies in animals have detected empagliflozin in breast milk. Due to lack of information regarding human use, women should not be treated with empagliflozin during pregnancy and breastfeeding.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Jardiance can be found on Jardiance's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

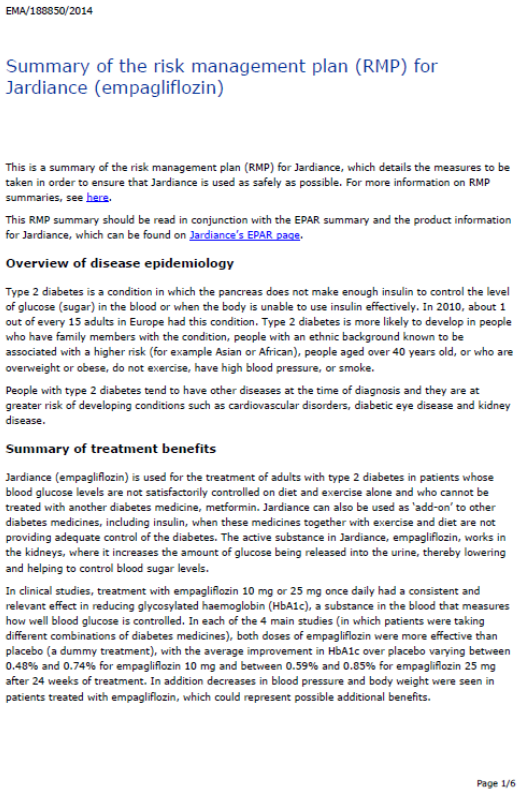
Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Long-term CV safety study 1245.25	To evaluate long-term cardiovascular safety of empagliflozin in patients with type 2 diabetes and increased cardiovascular risk.	Long-term safety (particularly cardiovascular), dyslipidaemia, use with GLP-1 analogues, urinary tract cancer, bone fracture, missing long-term safety information on melanoma	Started	Event driven, final results 4th quarter of 2015
PASS (1245.96) to assess the risk of renal and liver injury, urinary tract and genital infection	To evaluate the risk of urinary tract and genital infection, acute renal (kidney) and hepatic (liver) injury, resulting in hospitalisations, in empagliflozin-treated patients, compared with users of other diabetes treatment.	Urinary tract infection, genital infection, renal impairment, liver injury	Planned	Will depend on patient uptake; estimated submission date to be determined in the final study protocol

Survey for patients

1. If you were taking this medicine,

would you be interested in reading the RMP summary?

- ❑ Yes
- ❑ No



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2. If not, could you please state why?

- ❑ It’s too detailed
- ❑ It’s too long
- ❑ It’s not necessary
- ❑ It would make me worry about the side effects of the medicine
- ❑ Other:……..

3. If yes, could you please state why?

- ❑ It helps me understand how to take my medicine safely
- ❑ It shows that the safety of my medicine has been carefully considered
- ❑ Other:……..

4. Do you think the text is easy to understand?

- ❑ Yes
- ❑ No

5. If not, could you please state why? (please tick as many options as apply)

- ❑ It's too detailed
- ❑ It's too long
- ❑ It's not well explained
- ❑ The language is too technical
- ❑ The format makes it hard to read
- ❑ Other:……..

6. If you are interested in having this information, would it be useful to have it in your own language?

- ❑ Yes
- ❑ No

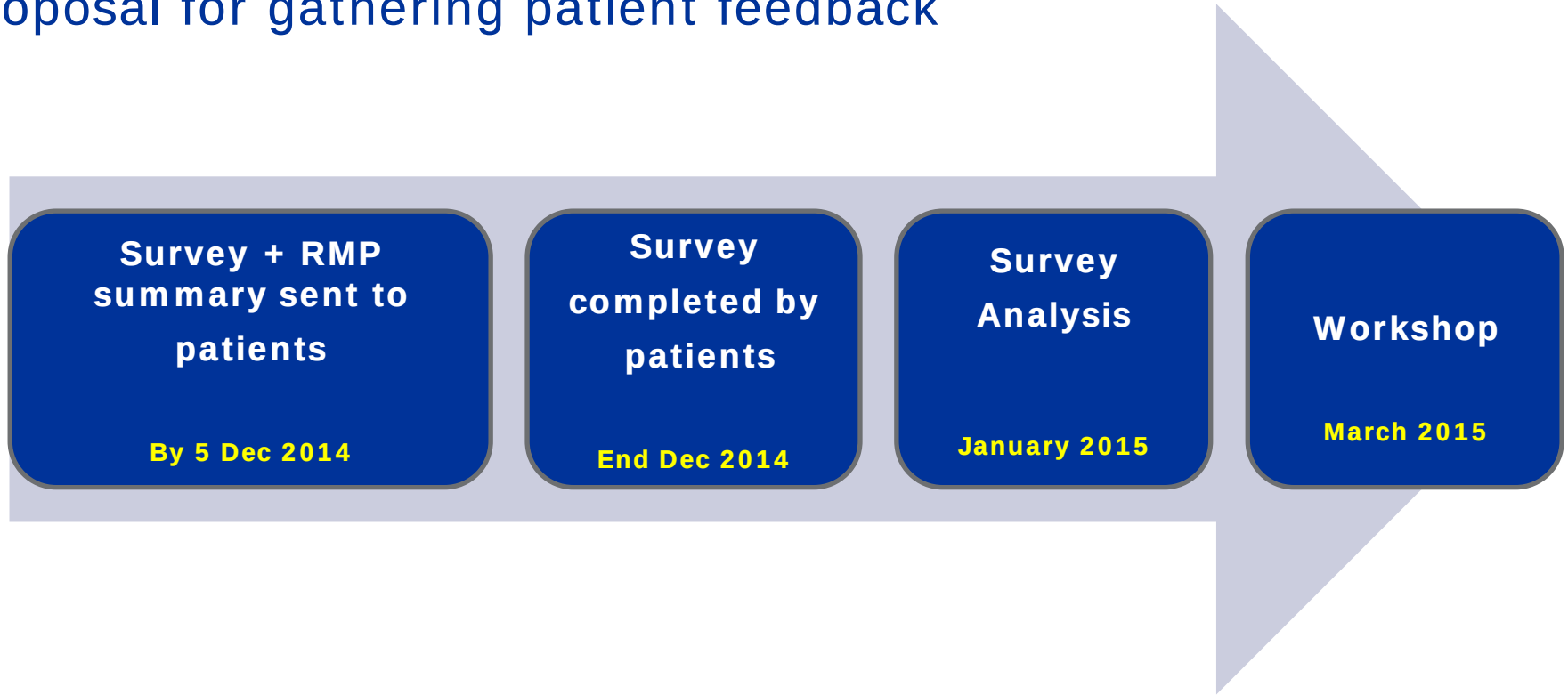
7. Do you think patients should be involved in the review of the summaries?

- ❑ Yes
- ❑ No

8. Please provide further comments to help us improve this document:

.....

Proposal for gathering patient feedback



Thank you!