

**UK Risk Management Plan for Glycopyrronium Bromide Oral Solutions
(Glycopyrronium bromide)**

RMP version to be assessed as part of this application:

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Summary of significant changes in this RMP:

- New proposed list of safety concerns and all relevant sections of the RMP updated, including update to the routine and additional risk minimisation measures relevant for each safety concern.
- Part V.2 of this RMP has been updated to align with PRAC recommendation on the non-interchangeability of glycopyrronium products without dose adjustment due to differences in bioavailability and strength.
- Updated post authorisation exposure to align with the latest submitted PBRER (DLP:14-Sep-2024).
- [REDACTED]
- [REDACTED]

QPPV name: [REDACTED]

QPPV signature: [REDACTED]

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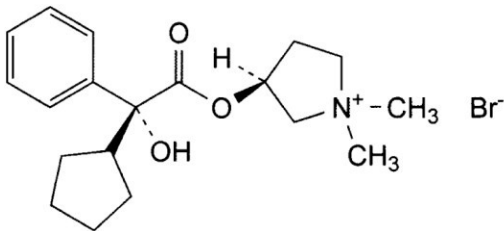
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List of abbreviations

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical classification system
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
GFR	Glomerular Filtration Rate
GVP	Good PharmacoVigilance Practices
HCP	Health Care Professional
INN	International Non-proprietary Name
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PL	Package Leaflet
QPPV	Qualified Person for Pharmacovigilance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Glycopyrronium bromide
Pharmacotherapeutic group(s) (ATC Code)	Drugs for functional gastrointestinal disorders, Synthetic anticholinergics, quaternary ammonium compounds (A03AB02)
Marketing Authorisation Holder	Colonis Pharma Limited
Medicinal products to which this RMP refers	█
Invented name(s) in the European Economic Area (EEA)	Glycopyrronium Bromide 1 mg/5 ml Oral Solution █
Marketing authorisation procedure	National
Brief description of the product	Chemical class Glycopyrronium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine. Glycopyrronium bromide is poorly absorbed from the gastrointestinal tract. Oral glycopyrronium bromide has low oral bioavailability; a mean of approximately 3% is found in plasma. Chemical name: (3RS)-3-[(2SR)-(2-Cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide CAS: 51186-83-5 Molecular formula: C₁₉H₂₈BrNO₃ Molecular mass: 398.3  and enantiomer Chemical Structure of Glycopyrronium Bromide Summary of mode of action Glycopyrronium bromide is a synthetic muscarinic anticholinergic agent that binds competitively to the muscarinic acetylcholine receptor. Like other anticholinergic (antimuscarinic) agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that

	respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and, to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions. Aside from differences in the CNS actions, the spectrum of pharmacological actions by glycopyrronium bromide is qualitatively similar to that of the naturally occurring alkaloids atropine and scopolamine, but differs with regard to duration and intensity. Within the peripheral nervous system, glycopyrronium bromide acts as a potent competitive antagonist at muscarinic receptors and attenuates physiological processes regulated by the parasympathetic nervous system, including predictable actions within the respiratory tract, gastrointestinal system, and heart. The highly polar quaternary ammonium group of glycopyrronium bromide limits its passage across lipid membranes, such as the blood-brain barrier. Important information about its composition Not applicable
Hyperlink to the Product Information	SmPC and PIL are hyperlinked
Indication(s) in the UK	Current (if applicable): <i>Glycopyrronium Bromide 1 mg/5 ml:</i> Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. [REDACTED] [REDACTED] [REDACTED] [REDACTED] Proposed (if applicable): Not applicable
Dosage in the UK	Current (if applicable): <i>Glycopyrronium Bromide 1 mg/5 ml:</i> Paediatric population - children and adolescents aged 3 years and older Glycopyrronium bromide oral solution is recommended for short-term intermittent use. The dosage of glycopyrronium bromide 1 mg/5 ml oral solution

Pharmaceutical form(s) and strengths	Current (if applicable): <i>Glycopyrronium Bromide 1 mg/5 ml:</i> Oral solution. Each 5 ml of oral solution contains 1 mg of glycopyrronium bromide (1mg/5ml). [REDACTED] [REDACTED] [REDACTED] [REDACTED]
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders

Incidence: The incidence of moderate or severe sialorrhoea cannot be estimated.

Prevalence: Prevalence of moderate or severe sialorrhoea in developmentally disabled children and adults, particularly those with cerebral palsy is estimated at between 10% and 37%.

The main existing treatment options: Attempts to control sialorrhoea in children with neurological dysfunction have included oromotor therapy, surgery, and medications. None are completely successful and may carry adverse effects. Drug therapy is aimed at decreasing the volume of oral saliva without addressing impaired swallowing. Key therapy is aimed at blockade of cholinergic muscarinic receptors. This reduces salivary volume but lack of selectivity results in undesirable central and peripheral nervous system effects, including restlessness, irritability, drowsiness, constipation, urinary retention and flushing. Glycopyrrolate is preferable as it has a limited potential for passage through the blood/brain barrier and therefore makes it more tolerable to patients with central nervous system impairments.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

indicate the consequences are both medical and psychosocial and include irritated and macerated facial skin, constant wetness and foul odour of clothing which interferes with personal relationships, lowering of self-esteem and restricted vocational options. Sialorrhoea is a constant source of frustration for patients and caregivers. As per the Drooling Rating Scale, the severity of drooling is classified as mild (wet lips only), moderate (wet lips and chin), severe (clothing becomes damp), and profuse (clothing, hands, tray and objects wet).

Important co-morbidities: Contraindications are in common with other antimuscarinics: angle-closure glaucoma; myasthenia gravis (large doses of quaternary ammonium compounds have been shown to block end plate nicotinic receptors); paralytic ileus; pyloric stenosis; prostatic enlargement; urinary retention; severe renal impairment (eGFR <30 ml/min/1.73m², including those with end-stage renal disease requiring dialysis, intestinal obstruction, pregnancy and breast-feeding; potassium chloride solid oral dose products and anticholinergic medicines.

Glycopyrronium bromide should be used with caution in gastro-oesophageal reflux disease, ulcerative colitis, acute myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, and cardiac surgery) because of the increase in heart rate produced by its administration, coronary artery disease and cardiac arrhythmias.

Due to the potential change to normal heart rhythm, glycopyrronium bromide should be used with caution in patients receiving inhalation anaesthesia.

As glycopyrronium bromide inhibits sweating [REDACTED], patients with increased temperature (especially children) should be observed closely. In the presence of a high environmental temperature, heat prostration (fever and heat stroke due to decreased sweating) can occur with use of glycopyrronium bromide oral solution.

Additional warnings are required with respect to use in children and adolescents due to anticipated anticholinesterase effects which may result in constipation, or urinary retention, or overheating due to inhibition of sweating.

The posology should ensure titration to an optimum dose to control hypersalivation without producing intolerable side effects.

Part II: Module SII - Non-clinical part of the safety specification

Not applicable

Part II: Module SIII - Clinical trial exposure

Not applicable

Part II: Module SIV - Populations not studied in clinical trials

Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]

[REDACTED]

[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]

SV.1.2 Exposure

[REDACTED]

[REDACTED]

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no known potential for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

This part was not included in the initial approved RMP.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Angle-closure glaucoma:

Risk-benefit impact: Reaction may have severe impact on the patient

Aggravation of myasthenia gravis:

Risk-benefit impact: Reaction may have severe impact on the patient

Aggravation of pyloric stenosis and paralytic ileus:

Risk-benefit impact: Reaction may have severe impact on the patient

Exacerbation of urinary urgency and retention in patients with prostatic enlargement:

Risk-benefit impact: Reaction may have severe impact on the patient

Tachycardia and its effect on existing cardiovascular conditions:

Risk-benefit impact: Reaction may have severe impact on the patient

Aggravation of gastro-oesophageal reflux disease:

Risk-benefit impact: Reaction may have severe impact on the patient

Suppression of intestinal motility in patients with ulcerative colitis:

Risk-benefit impact: Reaction may have severe impact on the patient

Intestinal obstruction in patients with ileostomy or colostomy:

Risk-benefit impact: Reaction may have severe impact on the patient

Change to normal heart rhythm in patients with inhalation anaesthesia:

Risk-benefit impact: Reaction may have severe impact on the patient

Fever or heat stroke in patients with hyperthermia:

Risk-benefit impact: Reaction may have severe impact on the patient

Prolongation of renal elimination in patients with uraemia:

Risk-benefit impact: Reaction may have severe impact on the patient

Enhanced effects due to altered hepatic and renal function in elderly patients:

Risk-benefit impact: Reaction may have severe impact on the patient

Enhanced antimuscarinic effects when used concomitantly with other antimuscarinic agents:

Risk-benefit impact: Interaction Reaction may have severe impact on the patient

Off-label paediatric use

Risk-benefit impact: Use in paediatric patients is not authorised

Use in children and adolescents (under 18 years of age):

Risk-benefit impact: The data is missing for paediatric population

Pregnancy and breastfeeding:

Risk-benefit impact: There are no, or limited, data from the use of glycopyrronium bromide in pregnant women. It is unknown whether glycopyrronium bromide or its metabolites are excreted in human milk.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

The PRAC Recommendation and Assessment Report on the PSUR (procedure number: EMEA/H/C/PSUSA/00010529/202409) for glycopyrronium products for sialorrhoea treatment was received on 10-Apr-2025, the following changes in the safety concerns are proposed:

Reclassified Risks:

- Important identified risk of Anticholinergic effects: Constipation, Urinary retention, Pneumonia, Risk of overheating; and Important potential risks of Cardiac disorders, Dental caries, CNS effects have been reclassified into Important potential risk "Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects" to align with the proposed PRAC recommendations.

Risk-benefit Impact: Glycopyrronium as with other antimuscarinic agents targets M-receptors and this may be associated with anticholinergic effects. The antimuscarinic effects are dose-related and are usually reversible when therapy is stopped. Careful dose titration and vigilance with regards to side effects is needed because agents such as glycopyrronium bromide have widespread effects manifested at all end organs that are governed by muscarinic receptors, and there is little selectivity in terms of blocking transmission at only the desired site. Specific known anticholinergic effects of glycopyrronium bromide include dryness of the mouth, reduced bronchial secretions, dilation of pupils with loss of accommodation, photophobia, flushing, inhibition of sweating, transient bradycardia followed by tachycardia with palpitations and arrhythmias, urinary urgency and retention, reduced gastrointestinal motility and tone. There are additional risk minimisation measures in place (Checklist for the Healthcare Professionals and Reminder Card for Caregivers) to further support prescribers and caregivers in the identification and management of the anticholinergic side effects. Refer to Part V.2 for details on additional risk minimisation measures in place.

This medicinal product is for prescription only.

Removed Risks:

- Important identified risk
 - Off-label use in patients below the age of 3 years due to the higher susceptibility to adverse effects

The risk is removed to align the safety concerns with the PRAC recommendation, as routine pharmacovigilance is considered sufficient to address it.

- Off label treatment of children with mild to moderate sialorrhoea

The risk is removed to align the safety concerns with the PRAC recommendation, as routine pharmacovigilance is considered sufficient to address it.

- Overdose including unintentional overdose due to 15 ml syringe (Present in RMP version 7.1)

This is covered under the important potential risk of 'Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects'.

- Missing information
 - Safety in long term use beyond 24 weeks

The safety concern is removed to align the safety concerns with the PRAC recommendation, as routine pharmacovigilance is considered sufficient to address it.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1.Presentation of important identified risks and important potential risks

Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects

Potential mechanisms:

Glycopyrronium has dose dependent anticholinergic properties due to its antagonistic effect on muscarinic receptors. Glycopyrronium bromide may produce the following effects, which are extensions of its fundamental pharmacological actions: constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, flushing, and dryness of the skin. The antimuscarinic effects are usually reversible when therapy is stopped.

Evidence source(s) and strength of evidence:

In the first study [REDACTED] most patients (n=122; 89 %) had at least one treatment-emergent adverse event, 47 % of which were deemed related to oral glycopyrrolate solution, with most being mild-to-moderate in intensity. The most commonly reported treatment-emergent adverse events occurring in ≥15 % of patients treated with glycopyrrolate oral solution (1 mg/5 ml) and at a greater frequency than placebo were constipation, vomiting, diarrhoea and flushing.

The two published randomised, placebo-controlled studies [REDACTED] report that between 13% to 15% of the patients had urinary retention while treated with glycopyrronium vs. 0% in the placebo group.

Pneumonia was reported as one of the treatment-emergent adverse events in the 24-week safety study conducted by [REDACTED]

In a pooled population of children with problem drooling associated with neurologic conditions, glycopyrrolate oral solution was associated with a moderate increase from baseline in mean systolic blood pressure (+3.4mmHg), a small decrease in mean diastolic blood pressure (-0.3mmHg), and a small (but clinically relevant) increase in mean heart rate (+1.9 beats/min; +10.5 beats/min) in the placebo-controlled study alone. No changes in mean respiratory rate or body temperature were observed, and the small increase in mean body weight (+1.15 kg) may be attributed to normal growth over a 6- month study period [REDACTED].

Since reduced salivation can increase the risk of oral cavities and periodontal diseases, it is important

that patients receive adequate daily dental hygiene and regular dental health checks.

The highly polar quaternary ammonium group of glycopyrronium bromide limits its passage across lipid membranes, such as the blood brain barrier. In adults, glycopyrronium does not seem to cross the blood brain barrier. However, in a study in children with hydrocephalus [REDACTED], glycopyrronium was detected in the CSF. This suggests that glycopyrronium might cross the blood brain barrier in children. In [REDACTED] 23% treated with glycopyrronium vs. 3% treated with placebo had behavioural changes.

Increased central nervous system effects have been reported in clinical trials including irritability; drowsiness; restlessness; overactivity; short attention span; frustration; mood changes; temper outbursts or explosive behaviour; excessive sensitivity; seriousness or sadness; frequent crying episodes; fearfulness. Behavioural changes should be monitored.

In studies supporting the paediatric indication, the adverse events related to typical anticholinergic effects were seen. There is no information on the incidence of anticholinergic adverse effects specifically due to dosing errors or medication errors.

Characterisation of the risk:

Anticholinergic effects such as urinary retention, constipation and overheating due to inhibition of sweat are dose dependent. There is no information on the severity of the urinary retention or if it is associated with increased incidence of urinary tract infections.

The frequencies of various anticholinergic effects of glycopyrronium range from 'very common' (constipation, behavioural changes) to 'common' (urinary retention, pneumonia), based on information in the SmPC.

Transient bradycardia (followed by tachycardia, palpitation and arrhythmias) are known adverse effects of glycopyrronium bromide. The frequency is unknown. There is no information to quantify the heart rate increase with glycopyrronium in children with neurological disorders.

The frequency of dental caries cannot be estimated.

The quaternary charge glycopyrronium has limited ability to penetrate the blood brain barrier, although the extent of penetration is unknown. Caution should be exercised in children with compromised blood brain barrier e.g. intraventricular shunt, brain tumour, encephalitis.

No case reporting anticholinergic side effects due to dosing error were confirmed based on data available in post marketing safety database, but the potential for dosing errors exists due to the product's posology and anticholinergic pharmacodynamics.

Risk factors and risk groups:

Many drugs have antimuscarinic effects; concomitant use of other anticholinergic medicinal products can increase side effects such as dry mouth, urine retention and constipation. The glycopyrronium bromide dosage may need to be decreased in patients receiving two or more antimuscarinic drugs concomitantly. The anticholinergic adverse effects are dose dependent. Existing fever and exposure to high temperature are potential risk factors for risk of overheating.

Patients with pre-existing cardiovascular disease(s) are considered at risk groups for cardiac disorders.

Paediatric population with severe sialorrhoea is a risk group for dental caries. The risk factors are non-

adequate daily dental hygiene and non-regular dental health checks.

CNS effects may occur in patients with a compromised blood brain barrier e.g. Intraventricular shunt, brain tumour, encephalitis.

Preventability:

Careful dose titration and vigilance with regards to side effects is needed because agents such as glycopyrronium bromide have widespread effects manifested at all end organs that are governed by muscarinic receptors, and there is little selectivity in terms of blocking transmission at only the desired site.

The carer should discontinue the treatment and seek advice from the prescriber in the event of constipation, urinary retention, pneumonia, allergic reaction, pyrexia, very hot weather and changes in behaviour. After evaluating the event, the prescriber will decide if treatment should remain discontinued or if the treatment should be re-started at a lower dose.

Prior to each increase in dose, review the tolerability of the current dose level with the patient's caregiver.

There are additional risk minimisation measures in place (Checklist for the Healthcare Professionals) and Reminder Card for Caregivers) to further support prescribers and caregivers in the identification and management of the anticholinergic side effects. Refer to Part V.2 for details on additional risk minimisation measures in place.

This medicinal product is for prescription only.

Impact on the risk-benefit balance of the product:

Anticholinergic adverse effects are well known and listed reactions for glycopyrronium.

Public health impact:

Low public health impact is expected.

SVII.3.2. Presentation of the missing information

Not applicable

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

There are no other routine pharmacovigilance activities beyond adverse reactions reporting and signal detection.

III.2 Additional pharmacovigilance activities

[illegible]

- [REDACTED]
- [REDACTED]

[REDACTED]

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██████████	██████████████████
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III.3 Summary Table of additional Pharmacovigilance activities

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]				
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]

Part IV: Plans for post-authorisation efficacy studies

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Anticholinergic effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects	Routine risk communication: – <i>SmPC section 4.2, 4.3, 4.4, 4.5, 4.8.</i> – <i>PIL section 2, 3, 4</i> Routine risk minimisation activities recommending specific clinical measures to address the risk: <i>SmPC section 4.2:</i> - <i>Recommendation for careful dose titration and to reduce the dose to previous dose if anticholinergic affects occur; use of syringe provided in the pack</i> - <i>Recommendation for use of specific dose recommendation for each product if switching between glycopyrronium products</i> <i>SmPC sections 4.4</i> - <i>Recommendation for monitoring of anticholinergic effects</i> Other routine risk minimisation measures beyond the Product Information: – Legal status: Prescription only medicine – Educational materials: • Checklist for Healthcare Professionals and reminder card for caregivers on company website and electronic medicines compendium.

V.2. Additional Risk Minimisation Measures

Checklist for Healthcare Professionals

Objectives:

- To provide information on the administration of Glycopyrronium Bromide oral solutions, specifically on the importance of accurate measure of the prescribed dose, the time of administration before the meals, the avoidance of the administration of glycopyrronium bromide with high fat meals, use of the oral syringe and the need to complete the administration table at the end of the reminder card for patient's carer to remind the carer of the correct dose to be given to the child.
- To alert the HCP that glycopyrronium products are not interchangeable without proper dose adjustment and to follow specific product dosage recommendations if it is necessary to change between products.
- To provide information on the management and minimisation of anticholinergic reactions, especially on management of constipation, urinary retention, pneumonia, risk of overheating, CNS effects or overdose; and on allergic reactions. In addition, the materials highlight the difficulty of the detection of anticholinergic reactions in the treated population and the need to decrease the dose to the previous one in case of suspicion of adverse drug reactions and contact the physician. The materials cover the need to avoid exposure to hot weather and overheating; risk of dental caries associated to reduced salivation and need for regular dental hygiene and dental checks and the requirement to check the pulse at regular intervals.

List of safety concerns addressed:

- Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects

Rationale for the additional risk minimisation activity:

To remind the prescriber about the risks associated with use of glycopyrronium bromide in paediatric population and to highlight important information to be brought to the attention of the patient/caregiver.

Target audience and planned distribution path:

The proposed prescribers are paediatric neurologists and general practitioners (GPs) who have prescribed glycopyrronium. The MAH proposes to distribute the additional materials via the electronic medicines compendium and company websites. Hardcopy package is available to healthcare professionals upon request.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Process evaluation is proposed as follows:

The distribution of the materials to the patient/ caregiver is done by the prescribing HCP on an entirely voluntarily basis. The Materials are available on emc and company websites. Hardcopy package is available upon request.

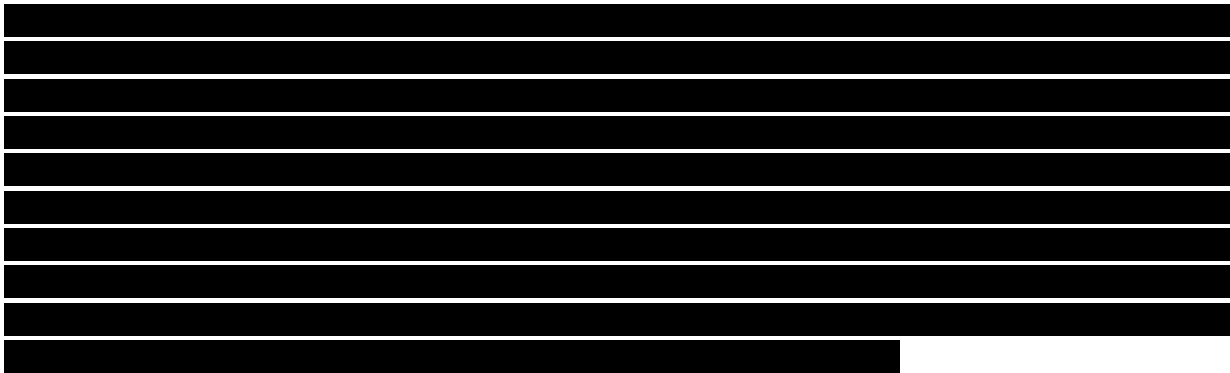
The number of distributed packages to the HCPs will continue to be tracked by the MAH.

The target distribution metrics are not applicable, as the HCP checklist hard copy package is distributed only upon request. Furthermore, the education materials for this product have been disseminated since 2020, indicating that HCPs who prescribe glycopyrronium are adequately informed about anticholinergic effects of the drug. Therefore, the effectiveness of this additional risk minimisation will be evaluated

solely through the routine signal detection activities.

An outcome evaluation is proposed as follows:

The risk of anticholinergic adverse drug reactions is dose dependent and increases with dose. Therefore, the dose titration and the compliance with dose schedule are important in order to manage and minimize risk of anticholinergic ADRs.



Reminder Card for Caregivers

Objectives:

- To provide information on the administration of glycopyrronium bromide, specifically on the accurate administration of the dose prescribed, the time of administration before the meals, the avoidance of the administration of glycopyrronium bromide with high fat meals, use of the oral syringe and the need to complete the administration table at the end of the reminder card for patient's carer to remind the carer of the correct dose to be given to the child.
- To alert the carer that Glycopyrronium oral solutions are not interchangeable without proper dose adjustment by the child's doctor.
- To provide information on the management and minimisation of anticholinergic reactions, especially on management of constipation, urinary retention, pneumonia, risk of overheating, CNS effects or overdose; and on allergic reactions. In addition, the materials highlight the difficulty of the detection of anticholinergic reactions in the treated population and the need to decrease the dose to the previous one in case of suspicion of adverse drug reactions and contact the physician. The materials cover the need to avoid exposure to hot weather and overheating; risk of dental caries associated to reduced salivation and need for regular dental hygiene and dental checks and the requirement to check the pulse at regular intervals.

List of safety concerns addressed:

- Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects

Rationale for the additional risk minimisation activity:

To support the parent/caregiver in recognising the risks associated with use of glycopyrronium bromide in paediatric population and to provide information about administration, management and minimisation of anticholinergic reactions.

Target audience and planned distribution path:

The caregivers of the patients which are to be prescribed glycopyrronium bromide. The information will be distributed to the patient/ caregiver from the prescribing HCP. The educational materials will also be available electronically on the eMC website.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Process evaluation is proposed as follows:

The prescribing HCPs will access the materials intended for them and for the patient/caregiver via emc. Hard copies are available upon request.

The target distribution metrics are not applicable, as the HCP checklist hard copy package is distributed only upon request. Furthermore, the education materials for this product have been disseminated since 2020, indicating that HCPs who prescribe glycopyrronium are adequately informed about anticholinergic effects of the drug. Therefore, the effectiveness of this additional risk minimisation will be evaluated solely through the routine signal detection activities.

An outcome evaluation is proposed as follows:

Anticholinergic adverse effects will be closely monitored through routine signal detection.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Anticholinergic effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects	Routine risk minimisation measures: <i>SmPC section 4.2:</i> - <i>Recommendation for careful dose titration and to reduce the dose to previous dose if anticholinergic affects occur; use of syringe provided in the pack</i> - <i>Recommendation for use of specific dose recommendation for each product if switching between glycopyrronium products</i> <i>SmPC sections 4.4</i> - <i>Recommendation for monitoring of anticholinergic effects</i> Other routine risk minimisation measures beyond the Product Information: - Legal status: Prescription only medicine - Educational materials: Checklist for Healthcare Professionals and reminder card for caregivers on company website and electronic medicines compendium.	Signal detection

Part VI: Summary of the risk management plan

Summary of risk management plan for Glycopyrronium Bromide Oral Solutions (glycopyrronium bromide)

This is a summary of the risk management plan (RMP) for Glycopyrronium Bromide Oral Solutions. The RMP details important risks of Glycopyrronium Bromide Oral Solutions, how these risks can be minimised, and how additional information will be obtained about Glycopyrronium Bromide Oral Solutions' risks.

Glycopyrronium Bromide Oral Solutions' summary of product characteristics (SmPC) and their package leaflets give essential information to healthcare professionals and patients on how Glycopyrronium Bromide Oral Solutions should be used.

Important new concerns or changes to the current ones will be included in updates of Glycopyrronium Bromide Oral Solutions RMP.

I. The medicine and what it is used for

Glycopyrronium Bromide 1mg/5ml [REDACTED]:

Glycopyrronium Bromide Oral Solution is authorised for symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders. It contains glycopyrronium bromide as the active substance and it is given by mouth as an oral solution.

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of glycopyrronium bromide Oral Solutions, together with measures to minimise such risks and the proposed studies for learning more about glycopyrronium bromide Oral Solutions' risks, are outlined below.

Measures to minimise the potential risks for the medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures. In the case of Glycopyrronium Bromide Oral Solutions, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

If important information that may affect the safe use of Glycopyrronium Bromide Oral Solutions is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Glycopyrronium Bromide Oral Solutions are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Glycopyrronium Bromide Oral Solution. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects.
Missing information	None

II.B Summary of important risks

Anticholinergic side effects due to dosing errors: constipation, urinary retention, pneumonia, risk of overheating, cardiac disorders, dental caries, CNS effects	
Evidence for linking the risk to the medicine	In the first study [REDACTED] most patients (n=122; 89 %) had at least one treatment-emergent adverse event, 47 % of which were deemed related to oral glycopyrrolate solution, with most being mild-to-moderate in intensity. The most commonly reported treatment-emergent adverse events occurring in ≥ 15 % of patients treated with glycopyrrolate oral solution (1 mg/5 ml) and a greater frequency than placebo were constipation, vomiting, diarrhoea and flushing. The two published randomised, placebo-controlled studies [REDACTED] [REDACTED] report that between 13% to 15% of the patients had urinary retention while

	treated with glycopyrronium vs. 0% in the placebo group. Pneumonia was reported as one of the treatment-emergent adverse events in the 24-week safety study conducted by [REDACTED] In a pooled population of children with problem drooling associated with neurologic conditions, glycopyrrolate oral solution was associated with a moderate increase from baseline in mean systolic blood pressure (+3.4mmHg), a small decrease in mean diastolic blood pressure (-0.3mmHg), and a small (but clinically relevant) increase in mean heart rate (+1.9 beats/min; +10.5 beats/min) in the placebo- controlled study alone. No changes in mean respiratory rate or body temperature were observed, and the small increase in mean body weight (+1.15 kg) may be attributed to normal growth over a 6- month study period [REDACTED] Since reduced salivation can increase the risk of oral cavities and periodontal diseases, it is important that patients receive adequate daily dental hygiene and regular dental health checks. The highly polar quaternary ammonium group of glycopyrronium bromide limits its passage across lipid membranes, such as the blood brain barrier. In adults, glycopyrronium does not seem to cross the blood brain barrier. However, in a study in children with hydrocephalus [REDACTED] glycopyrronium was detected in the CSF. This suggests that glycopyrronium might cross the blood brain barrier in children. In Mier et al. 2000, 23% treated with glycopyrronium vs. 3% treated with placebo had behavioural changes. Increased central nervous system effects have been reported in clinical trials including irritability; drowsiness; restlessness; overactivity; short attention span; frustration; mood changes; temper outbursts or explosive behaviour; excessive sensitivity; seriousness or sadness; frequent crying episodes; fearfulness. Behavioural changes should be monitored.
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	In studies supporting the paediatric indication, the adverse events related to typical anticholinergic effects were seen. There is no information on the incidence of anticholinergic adverse effects specifically due to dosing errors or medication errors.
Risk factors and risk groups	The concomitant use of other anticholinergic medicinal products can increase side-effects such as dry mouth, urine retention and constipation. The glycopyrronium bromide dosage may need to be decreased in patients receiving two or more antimuscarinic drugs concomitantly. The anticholinergic adverse effects are dose dependent. Patients with pre-existing cardiovascular disease(s) are considered at risk groups for cardiac disorders Paediatric population with severe sialorrhoea is a risk group for dental caries. The risk factors are non-adequate daily dental hygiene and non-regular dental health checks. CNS effects may occur in patients with a compromised blood brain barrier e.g. Intraventricular shunt, brain tumour, encephalitis.
Risk minimisation measures	Routine risk minimisation measures: <i>SmPC section 4.2:</i> - Recommendation for careful dose titration and to reduce the dose to previous dose if anticholinergic effects occur; use of syringe provided in the pack - Recommendation for use of specific dose recommendation for each product if switching between glycopyrronium products <i>SmPC sections 4.4</i> - Recommendation for monitoring of anticholinergic effects Other routine risk minimisation measures beyond the Product Information: ☐ Legal status: Prescription only medicine ☐ Educational materials: Checklist for Healthcare Professionals and reminder card for caregivers on company website and electronic medicines compendium.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Glycopyrronium Bromide Oral Solutions.

II.C.2 Other studies in post-authorisation development plan

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Part VII: Annexes

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Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Annex 7 - Other supporting data (including referenced material)

Annex 8 – Summary of changes to the risk management plan over time

Annex 1 – EudraVigilance Interface

Not Applicable

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

[illegible]

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

[REDACTED]

the 'information' and 'communication' fields. The 'information' field is defined as:

...the study of the processes of information production, distribution, access, use and evaluation, and the study of the social, cultural, economic and political contexts in which these processes take place. (p. 10)

The 'communication' field is defined as:

...the study of the processes of communication production, distribution, access, use and evaluation, and the study of the social, cultural, economic and political contexts in which these processes take place. (p. 10)

The 'information science' field is defined as:

...the study of the processes of information production, distribution, access, use and evaluation, and the study of the social, cultural, economic and political contexts in which these processes take place. (p. 10)

The 'information studies' field is defined as:

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The 'information technology' field is defined as:

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The 'information systems' field is defined as:

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The 'information management' field is defined as:

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The 'information ethics' field is defined as:

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The 'information education' field is defined as:

...the study of the processes of information production, distribution, access, use and evaluation, and the study of the social, cultural, economic and political contexts in which these processes take place. (p. 10)

the 1990s, the number of people in the UK who are employed in the public sector has increased by 1.5 million (1990–1999) and the number of people in the public sector has increased by 2.5 million (1990–1999) (Department of Health 2000).

There is a growing emphasis on the need to improve the efficiency of the public sector. The Department of Health (2000) has set out a number of targets for the public sector, including a 10% reduction in the number of people employed in the public sector by 2005. This has led to a number of initiatives to improve the efficiency of the public sector, including the introduction of the 'New Deal' for the public sector (Department of Health 2000).

The 'New Deal' for the public sector is a set of initiatives designed to improve the efficiency of the public sector. It includes a number of measures to reduce the number of people employed in the public sector, including the introduction of the 'New Deal' for the public sector (Department of Health 2000).

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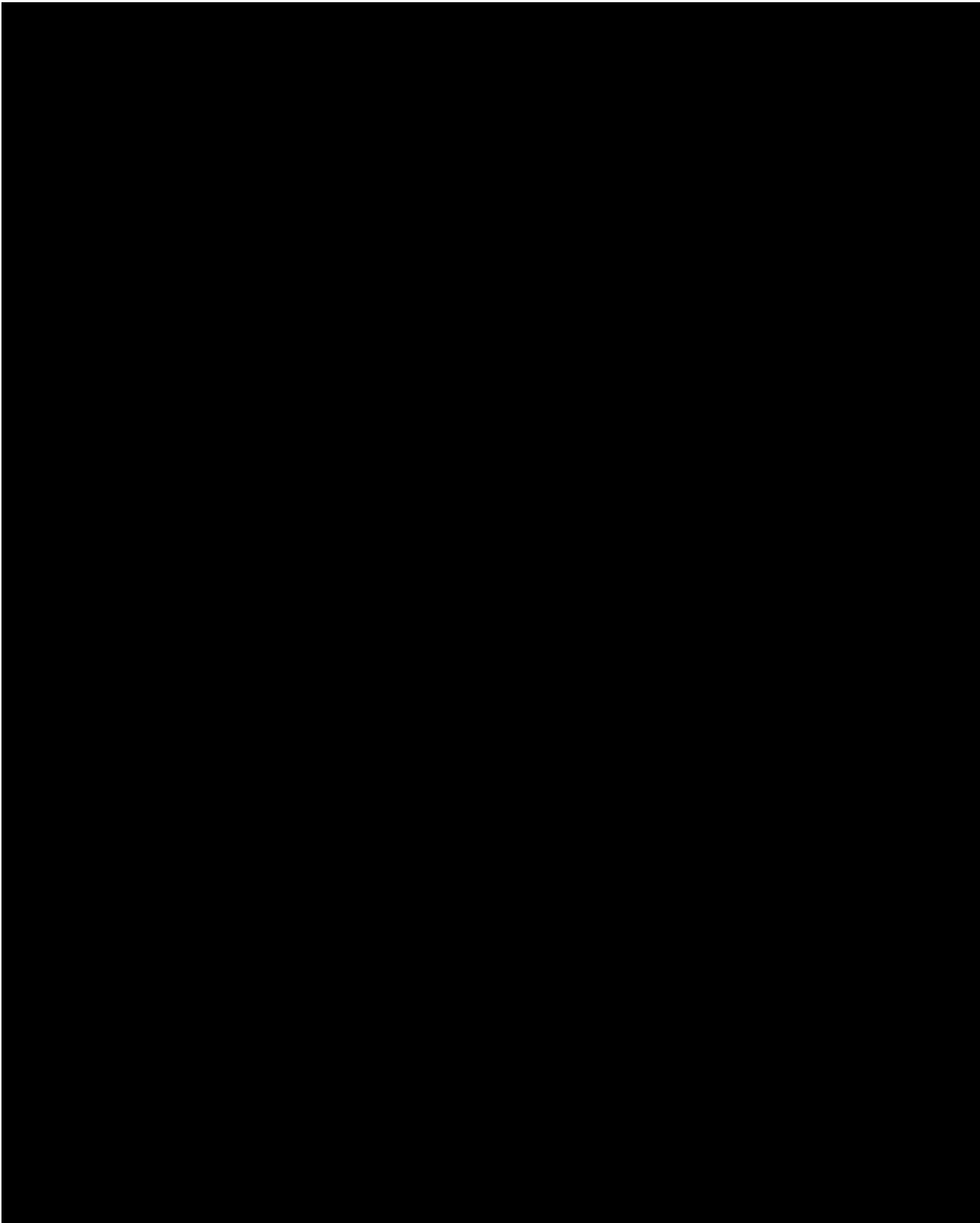
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the 1990s, the number of people in the UK who are employed in the public sector has increased by 1.5 million, from 2.5 million in 1980 to 4 million in 1995. The public sector has become a major employer in the UK, and its growth has been a major factor in the overall growth of the economy.

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the 1990s, the number of people in the UK who are employed in the public sector has increased by 1.5 million (1990–1999) (Department of Health 2000).

There is a growing emphasis on the importance of the public sector in the provision of health care services, and the need to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the efficiency and effectiveness of the public sector, including the introduction of competition and the restructuring of the public sector.

The public sector is also facing a number of challenges, including a growing demand for health care services, a shortage of health care professionals, and a need to improve the quality of care. These challenges are likely to continue to increase in the future, and it is therefore essential that the public sector is able to meet these challenges effectively.

The public sector is also facing a number of financial challenges, including a need to reduce costs and improve efficiency. This has led to a number of initiatives aimed at reducing costs and improving efficiency, including the introduction of competition and the restructuring of the public sector.

The public sector is also facing a number of political challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.

The public sector is also facing a number of social challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.

The public sector is also facing a number of environmental challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.

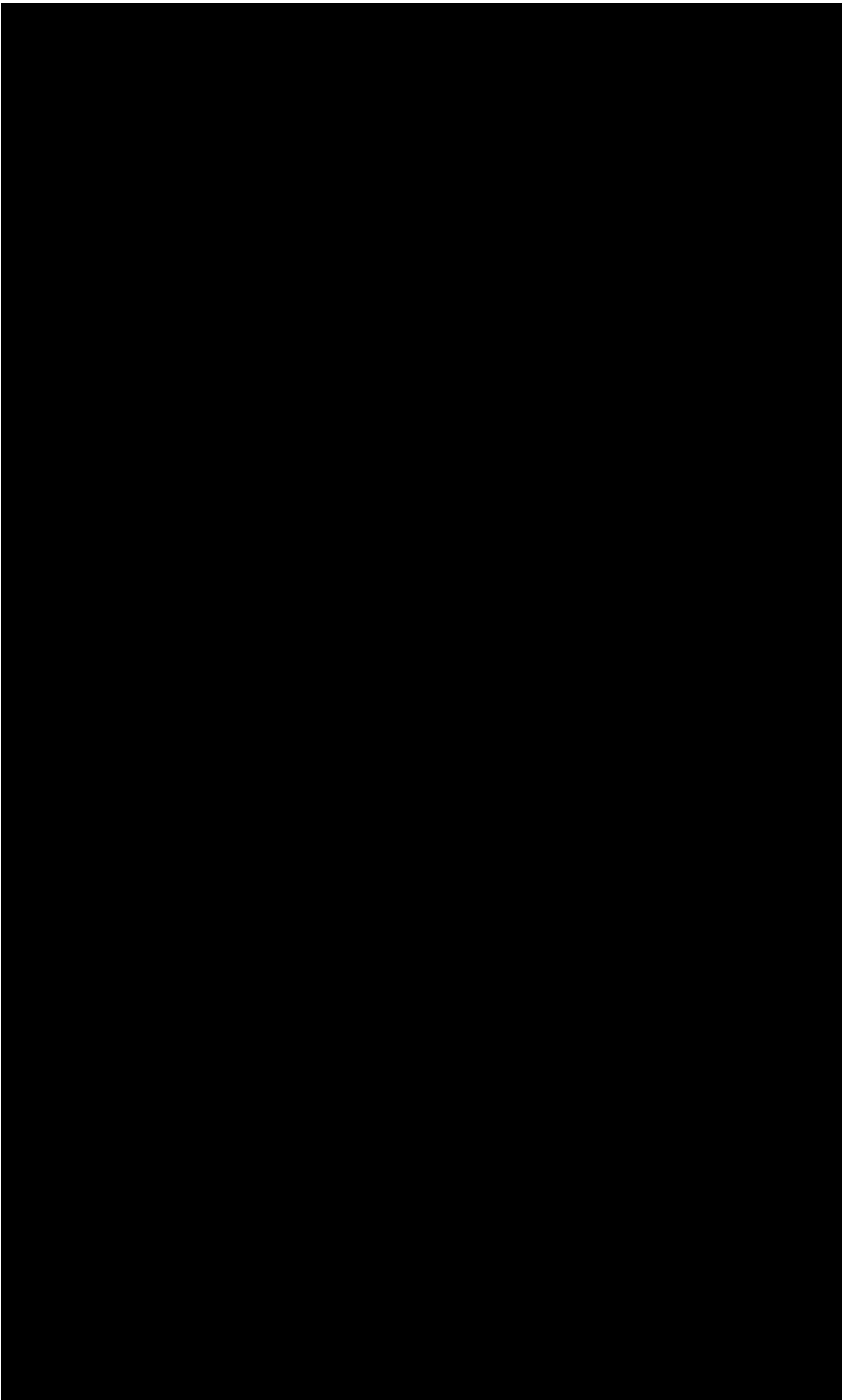
The public sector is also facing a number of cultural challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.

The public sector is also facing a number of technological challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.

The public sector is also facing a number of legal challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.

The public sector is also facing a number of ethical challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.

The public sector is also facing a number of moral challenges, including a need to improve the quality of care and to ensure that the public sector is able to meet the needs of the population. This has led to a number of initiatives aimed at improving the quality of care and ensuring that the public sector is able to meet the needs of the population.





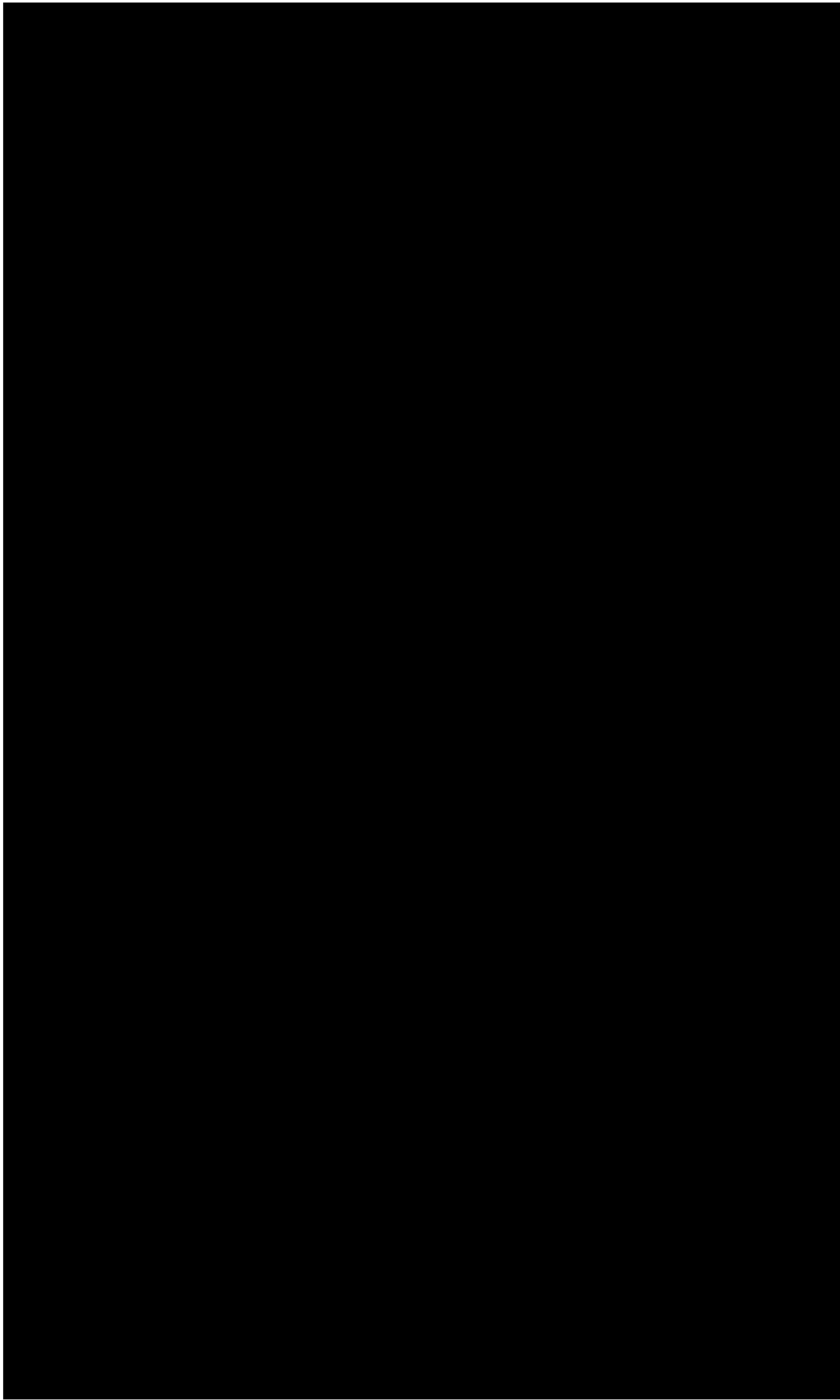
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The first part of the paper discusses the importance of the research and the objectives of the study. It then presents a literature review of the existing research on the topic. The next section describes the methodology used in the study, including the data collection and analysis techniques. The results of the study are then presented, followed by a discussion of the findings and their implications. The paper concludes with a summary of the main points and a list of references.

The research was conducted in a systematic and rigorous manner, following the principles of good research practice. The data was collected from a large and diverse sample of participants, and the analysis was conducted using advanced statistical techniques. The results of the study are presented in a clear and concise manner, and the implications of the findings are discussed in detail.

The findings of the study have important implications for the field of research. They suggest that there is a need for further research in this area, and that the results of this study can be used to inform policy and practice. The paper also highlights the importance of the research and the need for continued efforts to improve our understanding of the topic.

In conclusion, the paper provides a comprehensive overview of the research and its findings. It highlights the importance of the research and the need for continued efforts to improve our understanding of the topic. The results of the study are presented in a clear and concise manner, and the implications of the findings are discussed in detail.



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the 1990s, the number of people in the UK who are employed in the public sector has increased by 1.5 million, from 2.5 million in 1980 to 4 million in 1998. The public sector has also become an important employer of women, with 5.5 million women employed in the public sector in 1998, compared with 4.5 million in 1980.

There are a number of reasons why the public sector has become an important employer of women. One reason is that the public sector has a high proportion of women in its workforce. In 1998, 88% of the public sector workforce were women, compared with 78% in 1980. This is due to a number of factors, including the fact that the public sector has a high proportion of jobs that are traditionally held by women, such as teaching, nursing, and social work.

Another reason why the public sector has become an important employer of women is that it has a high proportion of jobs that are part-time or flexible. In 1998, 38% of the public sector workforce were employed on part-time or flexible contracts, compared with 28% in 1980. This is due to a number of factors, including the fact that the public sector has a high proportion of jobs that are traditionally held by women, such as teaching, nursing, and social work.

A third reason why the public sector has become an important employer of women is that it has a high proportion of jobs that are well paid. In 1998, the average salary of a public sector employee was £18,000, compared with £15,000 in 1980. This is due to a number of factors, including the fact that the public sector has a high proportion of jobs that are traditionally held by women, such as teaching, nursing, and social work.

There are a number of other reasons why the public sector has become an important employer of women. One reason is that the public sector has a high proportion of jobs that are secure. In 1998, 88% of the public sector workforce were employed on permanent contracts, compared with 78% in 1980. This is due to a number of factors, including the fact that the public sector has a high proportion of jobs that are traditionally held by women, such as teaching, nursing, and social work.

Another reason why the public sector has become an important employer of women is that it has a high proportion of jobs that are well located. In 1998, 38% of the public sector workforce were employed in London, compared with 28% in 1980. This is due to a number of factors, including the fact that the public sector has a high proportion of jobs that are traditionally held by women, such as teaching, nursing, and social work.

A third reason why the public sector has become an important employer of women is that it has a high proportion of jobs that are well matched to women's skills. In 1998, 88% of the public sector workforce were employed in jobs that required a degree or higher qualification, compared with 78% in 1980. This is due to a number of factors, including the fact that the public sector has a high proportion of jobs that are traditionally held by women, such as teaching, nursing, and social work.

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The first of these is the *Journal of the American Medical Association* (JAMA), which has been a leading voice in the medical profession for over a century. It is a weekly publication that covers a wide range of topics, from clinical medicine to public health. The second is the *New England Journal of Medicine* (NEJM), which is a leading journal in the field of clinical medicine. The third is the *Lancet*, which is a leading journal in the field of public health. The fourth is the *British Medical Journal* (BMJ), which is a leading journal in the field of clinical medicine. The fifth is the *Annals of Internal Medicine*, which is a leading journal in the field of clinical medicine. The sixth is the *Journal of the American Academy of Pediatrics* (JAAP), which is a leading journal in the field of pediatrics. The seventh is the *Journal of the American Geriatrics Society* (JAGS), which is a leading journal in the field of geriatrics. The eighth is the *Journal of the American Psychiatric Association* (JAPA), which is a leading journal in the field of psychiatry. The ninth is the *Journal of the American Society of Nephrology* (JASN), which is a leading journal in the field of nephrology. The tenth is the *Journal of the American Society of Hypertension* (JASH), which is a leading journal in the field of hypertension. The eleventh is the *Journal of the American Society of Endocrinology* (JASE), which is a leading journal in the field of endocrinology. The twelfth is the *Journal of the American Society of Human Genetics* (JASHG), which is a leading journal in the field of human genetics. The thirteenth is the *Journal of the American Society of Human Immunology* (JASHI), which is a leading journal in the field of human immunology. The fourteenth is the *Journal of the American Society of Human Microbiology* (JASHM), which is a leading journal in the field of human microbiology. The fifteenth is the *Journal of the American Society of Human Pathology* (JASHP), which is a leading journal in the field of human pathology. The sixteenth is the *Journal of the American Society of Human Physiology* (JASHPH), which is a leading journal in the field of human physiology. The seventeenth is the *Journal of the American Society of Human Pharmacology* (JASHPH), which is a leading journal in the field of human pharmacology. The eighteenth is the *Journal of the American Society of Human Toxicology* (JASHHT), which is a leading journal in the field of human toxicology. The nineteenth is the *Journal of the American Society of Human Nutrition* (JASHN), which is a leading journal in the field of human nutrition. The twentieth is the *Journal of the American Society of Human Psychology* (JASHPH), which is a leading journal in the field of human psychology. The twenty-first is the *Journal of the American Society of Human Sociology* (JASHS), which is a leading journal in the field of human sociology. The twenty-second is the *Journal of the American Society of Human Anthropology* (JASHA), which is a leading journal in the field of human anthropology. The twenty-third is the *Journal of the American Society of Human Linguistics* (JASHL), which is a leading journal in the field of human linguistics. The twenty-fourth is the *Journal of the American Society of Human Musicology* (JASHM), which is a leading journal in the field of human musicology. The twenty-fifth is the *Journal of the American Society of Human Art History* (JASHAH), which is a leading journal in the field of human art history. The twenty-sixth is the *Journal of the American Society of Human Literature* (JASHL), which is a leading journal in the field of human literature. The twenty-seventh is the *Journal of the American Society of Human History* (JASHH), which is a leading journal in the field of human history. The twenty-eighth is the *Journal of the American Society of Human Geography* (JASHG), which is a leading journal in the field of human geography. The twenty-ninth is the *Journal of the American Society of Human Economics* (JASHE), which is a leading journal in the field of human economics. The thirtieth is the *Journal of the American Society of Human Law* (JASHL), which is a leading journal in the field of human law. The thirty-first is the *Journal of the American Society of Human Education* (JASHE), which is a leading journal in the field of human education. The thirty-second is the *Journal of the American Society of Human Religion* (JASHR), which is a leading journal in the field of human religion. The thirty-third is the *Journal of the American Society of Human Philosophy* (JASHPH), which is a leading journal in the field of human philosophy. The thirty-fourth is the *Journal of the American Society of Human Science* (JASHS), which is a leading journal in the field of human science. The thirty-fifth is the *Journal of the American Society of Human Arts* (JASHA), which is a leading journal in the field of human arts. The thirty-sixth is the *Journal of the American Society of Human Sciences* (JASHS), which is a leading journal in the field of human sciences. The thirty-seventh is the *Journal of the American Society of Human Studies* (JASHS), which is a leading journal in the field of human studies. The thirty-eighth is the *Journal of the American Society of Human Research* (JASHR), which is a leading journal in the field of human research. The thirty-ninth is the *Journal of the American Society of Human Inquiry* (JASHI), which is a leading journal in the field of human inquiry. The fortieth is the *Journal of the American Society of Human Exploration* (JASHE), which is a leading journal in the field of human exploration. The forty-first is the *Journal of the American Society of Human Discovery* (JASHD), which is a leading journal in the field of human discovery. The forty-second is the *Journal of the American Society of Human Innovation* (JASHI), which is a leading journal in the field of human innovation. The forty-third is the *Journal of the American Society of Human Creativity* (JASHC), which is a leading journal in the field of human creativity. The forty-fourth is the *Journal of the American Society of Human Imagination* (JASHI), which is a leading journal in the field of human imagination. 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The fifty-first is the *Journal of the American Society of Human Perception* (JASHP), which is a leading journal in the field of human perception. The fifty-second is the *Journal of the American Society of Human Cognition* (JASHC), which is a leading journal in the field of human cognition. The fifty-third is the *Journal of the American Society of Human Memory* (JASHM), which is a leading journal in the field of human memory. The fifty-fourth is the *Journal of the American Society of Human Attention* (JASHA), which is a leading journal in the field of human attention. The fifty-fifth is the *Journal of the American Society of Human Awareness* (JASHA), which is a leading journal in the field of human awareness. The fifty-sixth is the *Journal of the American Society of Human Understanding* (JASHU), which is a leading journal in the field of human understanding. The fifty-seventh is the *Journal of the American Society of Human Knowledge* (JASHK), which is a leading journal in the field of human knowledge. The fifty-eighth is the *Journal of the American Society of Human Wisdom* (JASHW), which is a leading journal in the field of human wisdom. The fifty-ninth is the *Journal of the American Society of Human Virtue* (JASHV), which is a leading journal in the field of human virtue. The sixtieth is the *Journal of the American Society of Human Excellence* (JASHE), which is a leading journal in the field of human excellence. The sixty-first is the *Journal of the American Society of Human Achievement* (JASHA), which is a leading journal in the field of human achievement. The sixty-second is the *Journal of the American Society of Human Success* (JASHS), which is a leading journal in the field of human success. The sixty-third is the *Journal of the American Society of Human Fulfillment* (JASHF), which is a leading journal in the field of human fulfillment. The sixty-fourth is the *Journal of the American Society of Human Happiness* (JASHH), which is a leading journal in the field of human happiness. The sixty-fifth is the *Journal of the American Society of Human Well-being* (JASHW), which is a leading journal in the field of human well-being. The sixty-sixth is the *Journal of the American Society of Human Health* (JASHH), which is a leading journal in the field of human health. The sixty-seventh is the *Journal of the American Society of Human Longevity* (JASHL), which is a leading journal in the field of human longevity. The sixty-eighth is the *Journal of the American Society of Human Quality of Life* (JASHQL), which is a leading journal in the field of human quality of life. The sixty-ninth is the *Journal of the American Society of Human Life Satisfaction* (JASHLS), which is a leading journal in the field of human life satisfaction. The seventieth is the *Journal of the American Society of Human Life Purpose* (JASHLP), which is a leading journal in the field of human life purpose. The seventy-first is the *Journal of the American Society of Human Life Meaning* (JASHLM), which is a leading journal in the field of human life meaning. The seventy-second is the *Journal of the American Society of Human Life Value* (JASHLV), which is a leading journal in the field of human life value. The seventy-third is the *Journal of the American Society of Human Life Importance* (JASHLI), which is a leading journal in the field of human life importance. The seventy-fourth is the *Journal of the American Society of Human Life Significance* (JASHLS), which is a leading journal in the field of human life significance. The seventy-fifth is the *Journal of the American Society of Human Life Impact* (JASHLI), which is a leading journal in the field of human life impact. The seventy-sixth is the *Journal of the American Society of Human Life Legacy* (JASHL), which is a leading journal in the field of human life legacy. The seventy-seventh is the *Journal of the American Society of Human Life Contribution* (JASHC), which is a leading journal in the field of human life contribution. The seventy-eighth is the *Journal of the American Society of Human Life Service* (JASHS), which is a leading journal in the field of human life service. The seventy-ninth is the *Journal of the American Society of Human Life Leadership* (JASHL), which is a leading journal in the field of human life leadership. The eightieth is the *Journal of the American Society of Human Life Influence* (JASHI), which is a leading journal in the field of human life influence. The eighty-first is the *Journal of the American Society of Human Life Power* (JASHP), which is a leading journal in the field of human life power. The eighty-second is the *Journal of the American Society of Human Life Authority* (JASHA), which is a leading journal in the field of human life authority. The eighty-third is the *Journal of the American Society of Human Life Control* (JASHC), which is a leading journal in the field of human life control. The eighty-fourth is the *Journal of the American Society of Human Life Mastery* (JASHM), which is a leading journal in the field of human life mastery. The eighty-fifth is the *Journal of the American Society of Human Life Expertise* (JASHE), which is a leading journal in the field of human life expertise. The eighty-sixth is the *Journal of the American Society of Human Life Skill* (JASHS), which is a leading journal in the field of human life skill. The eighty-seventh is the *Journal of the American Society of Human Life Ability* (JASHA), which is a leading journal in the field of human life ability. The eighty-eighth is the *Journal of the American Society of Human Life Talent* (JASHT), which is a leading journal in the field of human life talent. The eighty-ninth is the *Journal of the American Society of Human Life Gift* (JASHG), which is a leading journal in the field of human life gift. The ninetieth is the *Journal of the American Society of Human Life Potential* (JASHP), which is a leading journal in the field of human life potential. The hundredth is the *Journal of the American Society of Human Life Possibility* (JASHP), which is a leading journal in the field of human life possibility.



13 References

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP Checklist for Study Protocols

Annex 3. Additional Information

Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms

None proposed

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

Not Applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Draft key messages of the additional risk minimisation measures

The physician educational material will contain:

- The Summary of Product Characteristics
- Remarks on the importance of reporting on specific adverse drug reactions, namely: urinary retention, constipation, pneumonia, allergic reactions, dental caries, cardiovascular effects, CNS effect and overheating

Checklist for Healthcare Professionals, will contain the following key messages:

- a. Information on the administration of Glycopyrronium Bromide Oral Solution
- b. Non-interchangeability without specific product's proper dose adjustment.
- c. Management and minimisation of anticholinergic reactions

The patient information pack will contain:

- Patient information leaflet

The reminder card for patient's carer, will contain the following key messages:

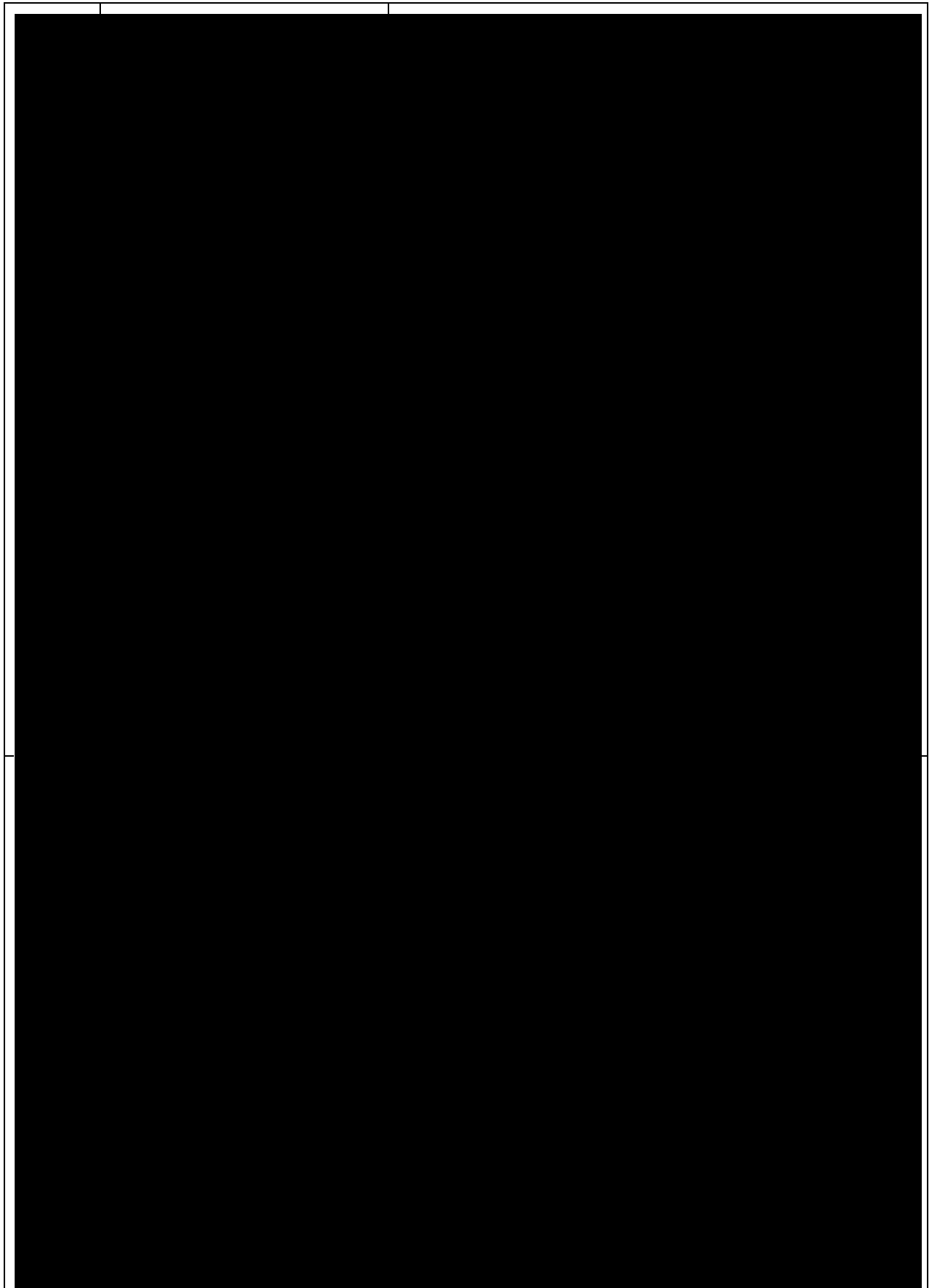
- a. Information on the administration of Glycopyrronium Bromide Oral Solution
- b. Non-interchangeability without doctor's prescription and proper dose adjustment.
- c. Management and minimisation of anticholinergic reactions

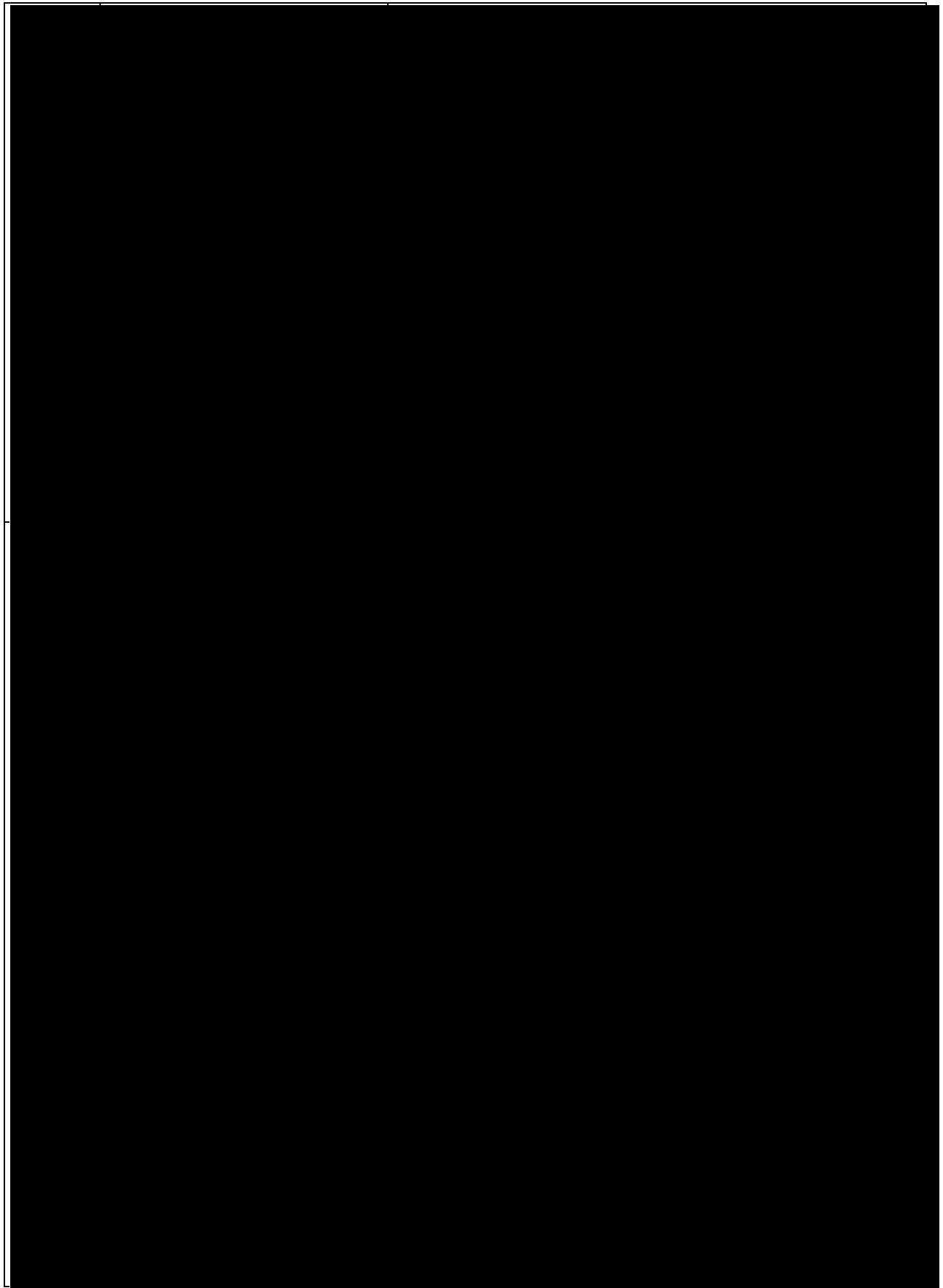
Annex 7 - Other supporting data (including referenced material)

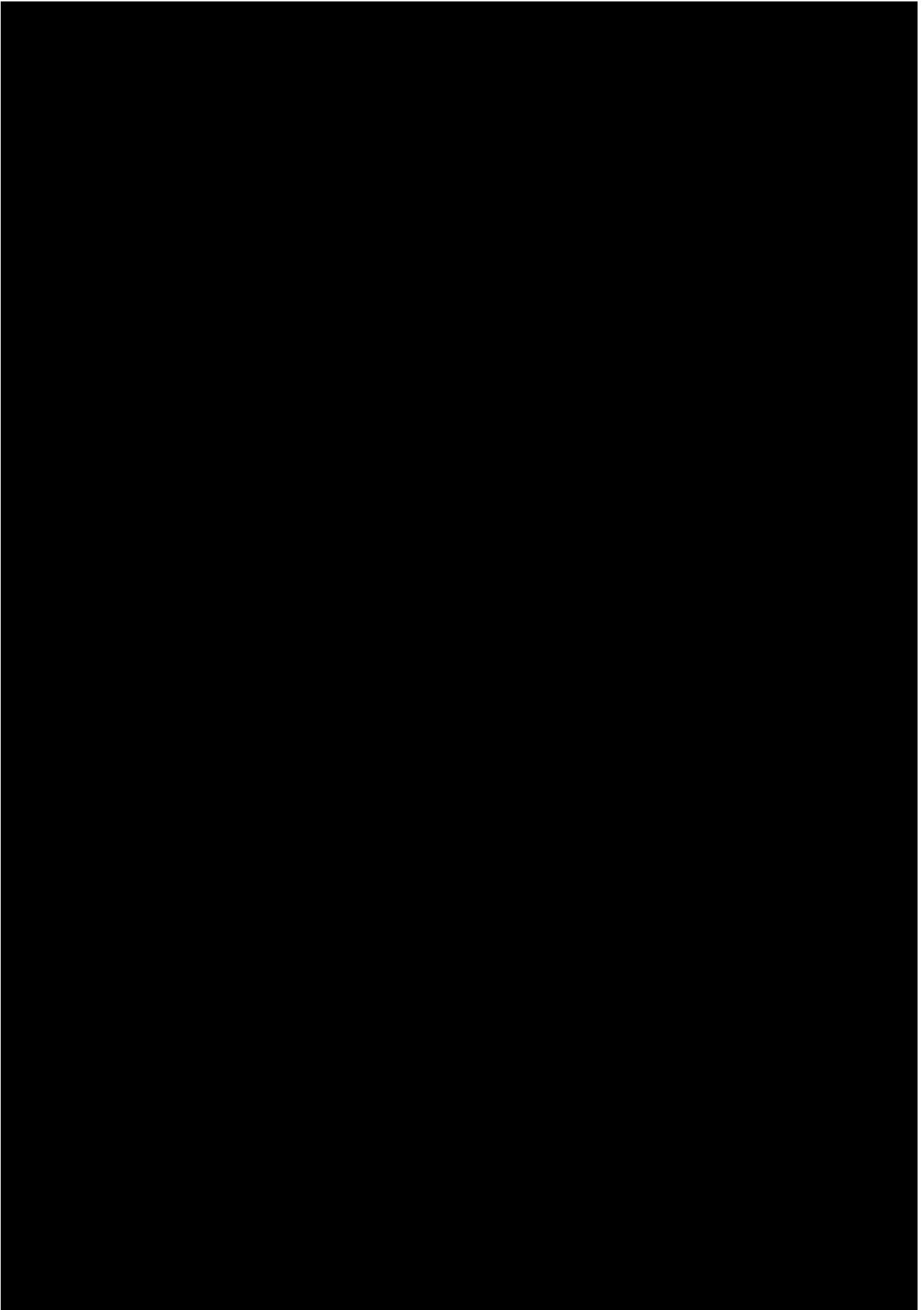
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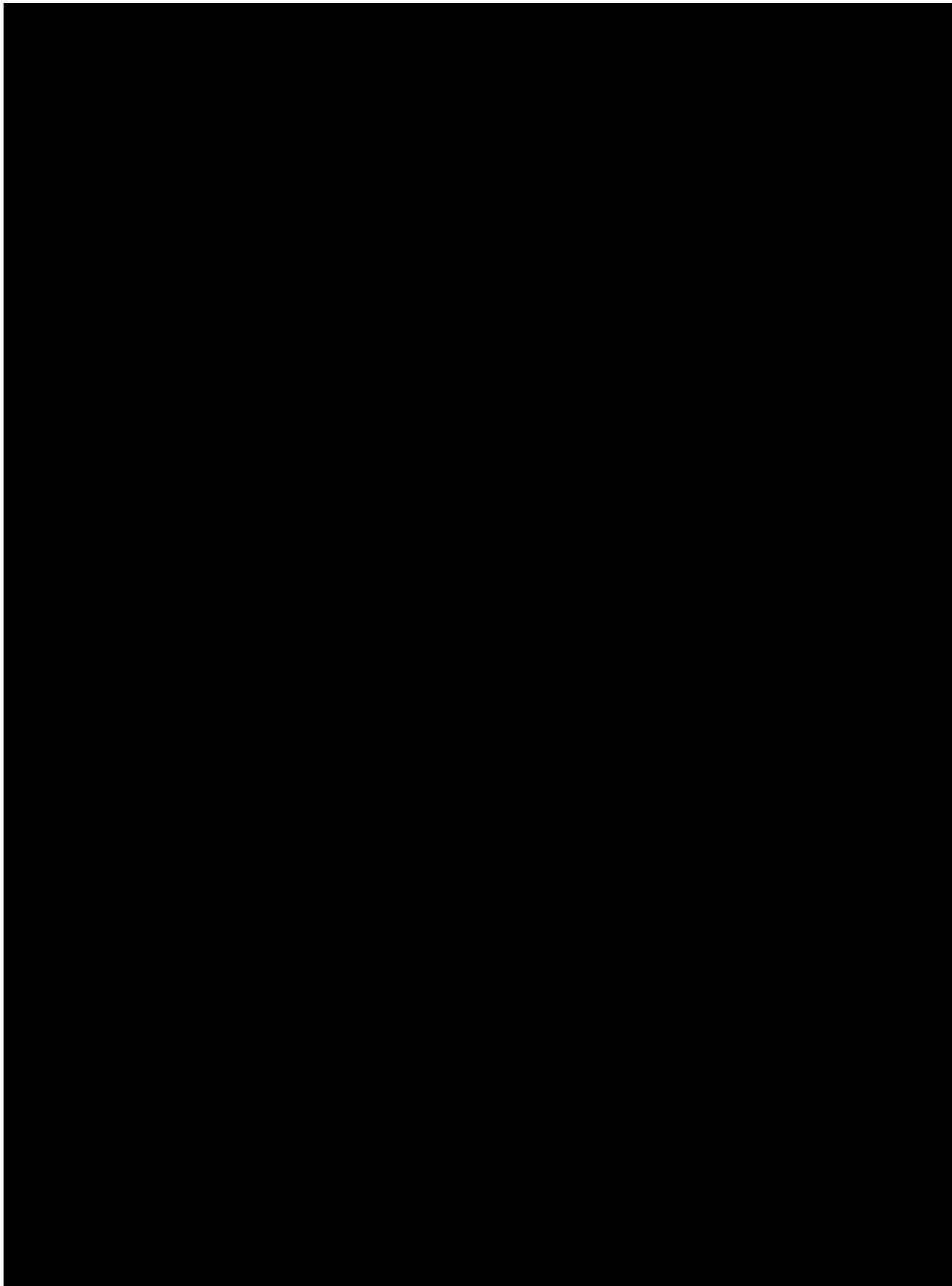
Annex 8 – Summary of changes to the risk management plan over time

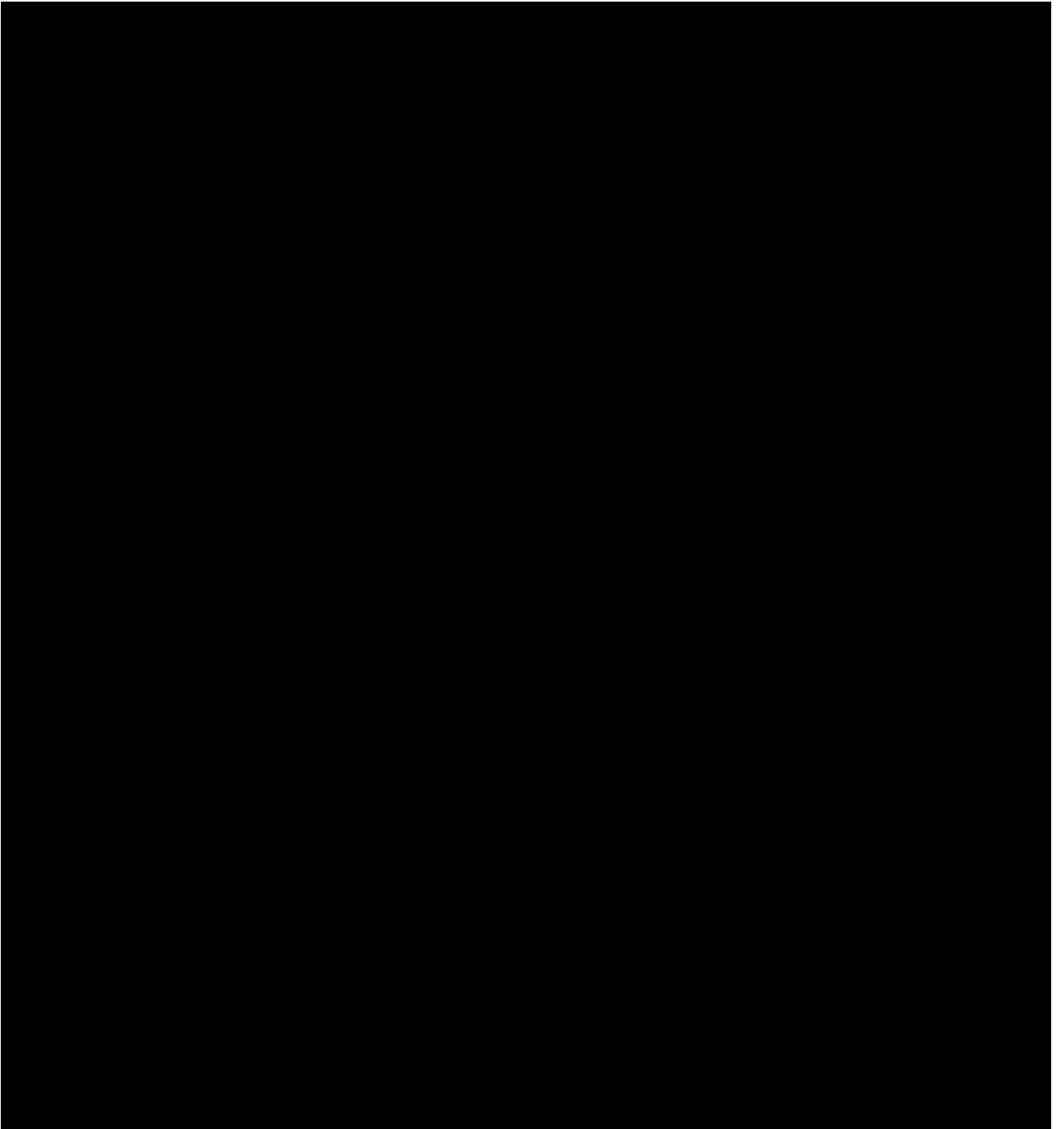
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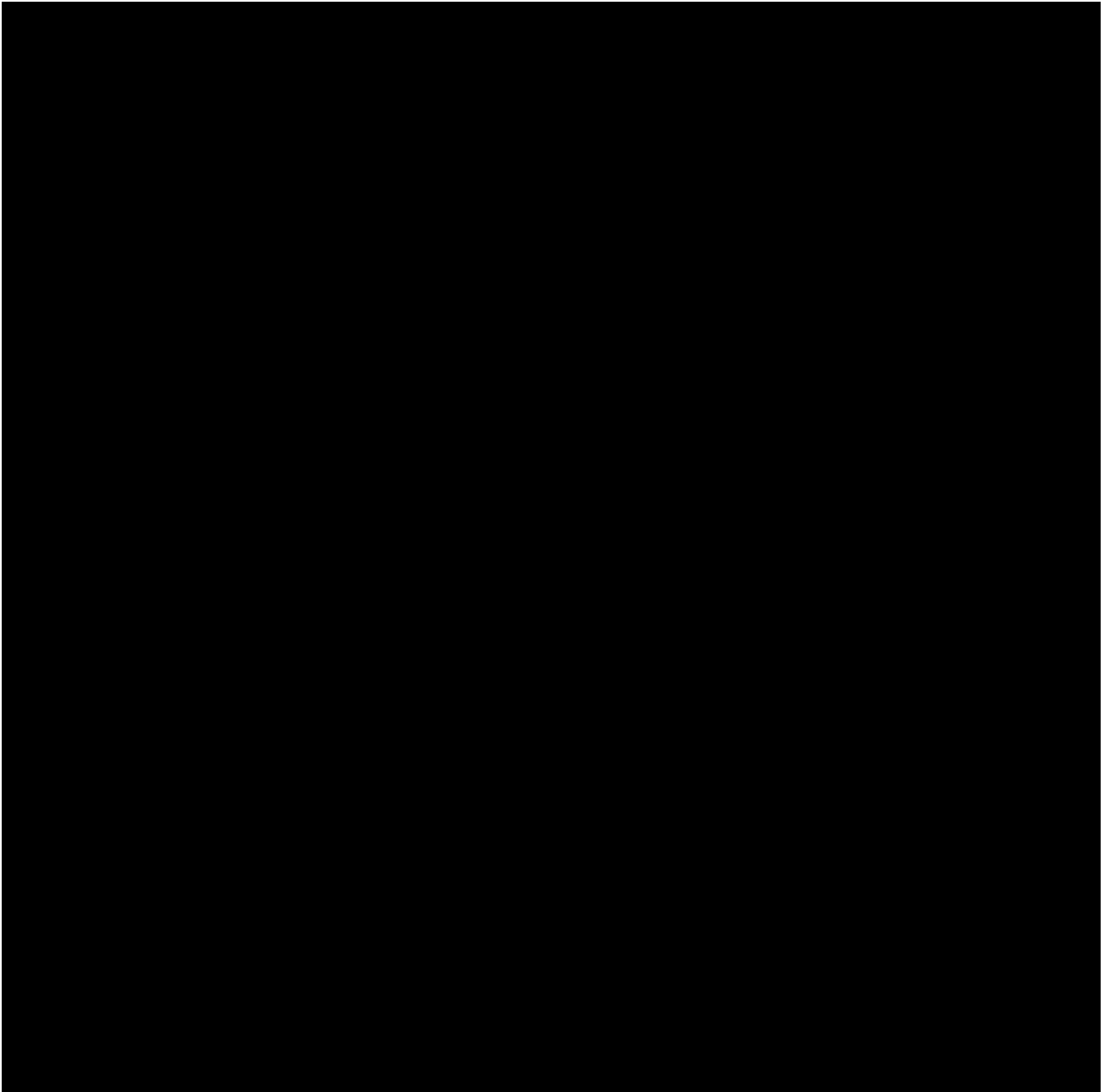












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