NOT FOR PUBLICATION

COMMISSION ON HUMAN MEDICINES

VACCINE BENEFIT RISK EXPERT WORKING GROUP

Title of paper: Update COVID-19 Vaccines and risk of thromboembolic events with concurrent thrombocytopenia **Type of paper:** For advice

Active(s) rINN	AstraZeneca COVID-19 vaccine
Product name(s)	
Marketing Authorisation Holder(s)	AstraZeneca
Legal status	Prescription only medicines
Therapeutic classification **(ATC code)**	
Previous assessments	
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1. Introduction

The Pfizer/BioNTech COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 2 December 2020. It is estimated that over 10 million doses have been administered in the UK as of 14 March 2021. The AstraZeneca COVID-19 vaccine was authorised for use under Regulation 174 by the MHRA on 30 December 2020, and over 13 million doses have been administered in the UK as of 14 March 2021.

Following the previous discission of available evidence at the COVID-19 VBR EWG held on 17 March 2021, it was considered that the available evidence did not identify a causal association between venous thromboembolic events and the AstraZeneca COVID-19 vaccine. However, the MHRA was continuing to further evaluate cases of cerebral venous sinus thromboses (CVST) with thrombocytopenia. Further actions were agreed, including a call for reporting of cases via the Yellow Card scheme, further work with expert haematologists on gathering relevant information, and rapid review of this information with a view to further discussion with the EWG. A statement was issued by the MHEA on 18 March 2021 to communicate this, and to reiterate that the benefit-risk of COVID-19 vaccine AstraZeneca remained positive (https://www.gov.uk/government/news/uk-regulator-confirms-that-people-should-continue-to-receive-the-covid-19-vaccine-astrazeneca).

The European Medicine's Agency's (EMA) preliminary review on the signal also concluded last week. On 18 March 2021, the EMA produced a similar statement, noting the positive benefit-risk and the lack of an association with the overall risk of thromboembolic events, but noting the possible association with rare events of thrombosis with thrombocytopenia. In their statement, the EMA references 7 cases of disseminated intravascular coagulation (DIC) and 18 cases of CVST in the context of 20 million people receiving the vaccine across the UK and EEA.

This paper provides an update of the available data since the previous discussion; this includes UK cases and known details about cases from the EU/ worldwide.

2. Case summaries and discussion

The evaluation focused on any thromboembolic events reported in conjunction with thrombocytopenia, for completeness this included arterial and venous emboli with a data lock point of the 21st of March 2021. Cases were considered for inclusion if the reporter considered there to be both a thrombosis and a thrombocytopenia. All platelet levels in the cases identified were noted to be under the proposed threshold of 150 x 10^9/L.

To date these have only been reported with the AstraZeneca vaccine. There were 28 cases of interest in total. These cases are presented in the table in Annex 1.

Of the 28 cases reporting thrombosis in conjunction with thrombocytopenia, 18 reported CVST, 2 reported cortical venous thrombosis, 6 reported pulmonary embolus, 1 reported portal vein thrombosis and 1 reported multiple arterial emboli (femoral/ renal/ superior mesenteric artery). Of note, in a proportion (6 cases), the thrombosis affected more than one vascular system:

- 1 CVST case reported [redacted]
- 1 cortical vein thrombosis case reports [redacted]
- 1 CVST case reports [redacted]
- 1 CVST case reports [redacted]
- 1 PE case also reported [redacted]
- 1PE case reports [redacted]
-

Cerebral thromboses events with thrombocytopenia

Demographics

Of the events reporting CVST and cortical venous thrombosis (20 in total), the ages ranged from 19 to 70 (median 34, mean 40.9). The majority were in patients under 50 years of age (15/20), age was unknown in 1 case. 11 were female and 9 were male. Just over half the cases (12/20) were described as British/ white British, and ethnicity was not reported in 6.

Time to onset

Time to onset in these cases ranged between 5- 16 days (median 10 days, mean 10.5 days). 17 cases stated that events occurred in relation to first doses, dose was not stated in the remaining cases.

Comorbidities or pre-existing risk factors

11/20 cases provided information on comorbidities or past medical history.

Comorbidities of note that were reported included primary sclerosing cholangitis and autoimmune hepatitis anorexia (presumed anorexia nervosa, , inflammatory bowel disease with use of mesalazine and azathioprine) and fibromyalgia). These are also potential risk factors for thrombotic events. Other medical history reported which were likely of lesser significance included a ventricular septal defect ( ) which had not caused any significant medical issues and osteoarthritis with prediabetes. 5 were reported as having no medical history of note. In the remaining cases, no information on comorbidities/ past medical history was given, despite follow up questioning.

Information was also sought on any additional concurrent risk factors for thrombocytopenia or thrombophilia. Malignancy was reported as suspected in one individual however limited information was provided about the type of malignancy and this diagnosis was not confirmed. In 2 patients ( ) anti-phospholipid syndrome was queried as a diagnosis. Two additionally reported weakly positive lupus tests.

In 3 cases relatively detailed information excluding potential risk factors for both thrombocytopenia and thrombosis were provided (events excluded are provided in the footnote to the table), 5 other cases provided less detailed information on risk factors excluded, for example one case In the remaining 7 cases no information on thrombocytopenic or thrombophilic risk was provided. Information on pregnancy was not provided for any patient .

Information on mechanism

A minority of cases provided attempted to elucidate a possible mechanism. One case was positive for anti-PF4 antibodies, but this does not appear to have been tested in most of cases. One case states that “reliable” testing for HIT-like syndrome was negative, although details on the assay used were not provided.

Platelet count

Platelet count was provided in 11/20 cases, this ranged from 10 to 101 x 10^9/L, with 9 of the cases describing platelets <50 x 10^9/L. It was unclear in some cases whether these were nadir platelets and apart from one case describing a fall in platelets from 64 to 42 no trend in platelets was provided.

3 cases additionally report a few other parameters of coagulation. This included 2 cases where PT, APTT and INR were within normal range. Two cases with normal clotting times also reported either

mildly reduced fibrinogen or fibrinogen at the lower end of the range, one reports normal clotting times with normal fibrinogen. One case [redacted]

COVID-19 status

[redacted] 3 patients report negative PCR tests which imply no current infection. [redacted]

1 patient [redacted]

In the remaining cases it was not clear if tests for current COVID-19 had been performed, some stated the patient was COVID-19 negative but the basis for this is uncertain. Previous COVID-19 infection was largely not specifically checked for.

Concomitant medications and treatment

In terms of concomitant medications, of note 1 case [redacted] n 11/16 cases no information was provided.

For treatment of the thrombotic events, use of low molecular weight or intravenous heparin as treatment was mentioned in only 3 cases. The picture of recovery is mixed. 1 case describes [redacted] and in the remaining cases information on treatment was not provided.

For treatment of thrombocytopenia, platelet transfusion was used in 2 cases ([redacted]

IVIG and steroids were used in [redacted] with no response to treatment. Another patient [redacted]) received a platelet transfusion, IVIG and steroids and is reported as neurologically stable. Other cases did not report treatment for thrombocytopenia.

Outcomes

7 events were fatal, 5 were individuals under 50 years of age (aged [redacted] and 2 were aged [redacted] respectively.

3 patients, a[redacted] were reported as recovering.

8 patients were reported as not recovered, stable or requiring on-going care.

1 has been discharged.

Outcome as unknown for 1 patient.

Other thromboses with thrombocytopenia

There are 8 cases in total in this category, 6 involve PEs. 1 PE additionally reported splenic vein thrombosis and multiple cerebral infarcts while another reports bilateral PEs [redacted] The remaining 2 cases report a portal vein thrombosis in one and multiple arterial thrombi (femoral, renal and superior mesenteric) in the other.

Demographics

4 PE cases were in patients aged 60-73, with age unknown in 2. 4 were female with ethnicity described as British, [redacted] The remaining cases were in 2 females and 1 male of unknown ethnicity.

The portal vein thrombosis occurred in a [redacted] The arterial emboli occurred in a [redacted]

All events occurred after the first dose.

Time to onset

In the PEs 3 cases time to onset was reported as 9 days and unknown in 2, [redacted]

Comorbidities or pre-existing risk factors

The case with the [redacted]

In the remaining PE cases, no information was provided on concurrent or pre-existing risk factors.

For the portal venous thrombosis, [redacted]

No information was provided on comorbidities or past medical history for the arterial emboli case.

Platelet count

A trend in daily platelet count was provided for the arterial embolus case, indicating [redacted]

Mechanisms investigated

One PE case was considered to be possible DIC, [redacted]

One PE cased describes [redacted]

In the patient with portal venous thrombosis [redacted]

The patient with femoral, renal and superior mesenteric artery thrombus [redacted]

COVID status

Patients were described as COVID-19 negative but it was unclear how this was ascertained. No PCR results were provided. No patients had serology.

Concomitant medications and treatment

In 1 PE case, no evidently prothrombotic or thrombocytopenia inducing medication was reported, 1 patient [redacted]; thrombocytopenia is an associated event for these medications. 1 patient [redacted] Concomitant medication was not reported in the other PE cases. As treatment, 2 received platelet infusion, 1 of which also received [redacted] The patient with [redacted]

1 PE case [redacted]

No information about concomitant medications or treatment were provided in the other 2 PE cases.

The patient with portal vein thrombosis [redacted]

Outcomes

In 1 PE case the patient has been discharged, 1 is recovering with residual shortness of breath and the other four cases have not recovered.

The portal vein thrombosis patient has been discharged.

The patient with multiple arterial emboli has not recovered.

No case was fatal.

3. Worldwide cases case summary and discussion

Cases from outside the UK for which the MHRA has details are summarised below.

Cases from [redacted]

4 cases were reported from [redacted] 3 of which reported cerebral venous sinus thromboses with thrombocytopenia and 1 which reported a portal vein thrombosis with thrombocytopenia. The CVST cases involved female patients aged [redacted] respectively. 2 of the cases also involved thrombosis of the jugular vein. The portal vein case [redacted]

The events occurred 8 to 10 days after vaccination. In 3 of the 4 CVST cases the patients were on contraception ([redacted] as risk factors for thrombosis.

Platelet count was provided in 2 CVST cases (37 and 119 x 10^9/L) and in the portal venous thrombosis case 10 x 10^9/L. One CVST case [redacted] nd died. Of the other 2 CVST cases [redacted]

None of the cases provide information regarding previous COVID-19 infection or current COVID-19 status. Information on whether the event occurred after the first or second dose was not provided.

Cases from [redacted]

7 cases, all of CVST with thrombocytopenia, have been reported from [redacted] All were female and the age range was 22 to 45 (median age 43), time to onset 4 to 14 days.

Potential confounding factors were provided in 3 cases, 1 case describes an unspecified rare genetic disorder known to cause increased bleeding, 1 one was on oral contraceptives, 1 case had numerous thrombophilic risk factors (Factor V Leiden mutation, cardiolipin antibody, VWF type 1).

Platelet counts were provided in 4 patients (nadir platelets 9, 16,23,75).

No information on treatment provided has been given. No information on pregnancy has been provided. 2 patients were described as SARS-CoV-2 negative, no information on past or current COVID-19 infection was otherwise provided.

Cases from [redacted]

One case in a [redacted] describes ischemic cerebral infarction, thrombocytopenia, systemic hypercoagulative disorder and disseminated intravascular coagulation. [redacted] he thrombocytopenia was considered secondary to thrombosis and interpreted as a consumptive thrombocytopenia rather than immune-dependent. [redacted] he patient [redacted] died.

Cases from AZ

In addition to the cases identified by the EMA at PRAC on the 16th March 2021, there are an additional 3 non-UK cases reporting embolic/thrombotic alongside thrombocytopenia. Two cases report CVST alongside thrombocytopenia, one case reports DIC alongside thrombocytopenia.

Of the three cases of interest, two cases report possible confounding factors of concurrent chronic hepatitis B infection and pre-existing Hashimoto's disease. One of the cases of interest is male and two female; all are under 55 years of age. The time to onset are all 14 days or less. Prior or concurrent COVID-19 infection is not reported in any of these cases. None of the cases identify whether the events are after the first or second dose.

Summary of additional non-UK cases identified by AstraZeneca reporting thrombocytopenia and thrombosis/embolism or bleeding events, as of 16th March 2021

Country of origin	Patient age/sex	ADRs	Time to onset	Summary
[redacted]	[redacted]	Ischaemic stroke; Thrombocytopenia; Disseminated intravascular coagulation/	Several - 10 days	Fatal case. [redacted]
[redacted]	[redacted]	Thrombocytopenia, Cerebral venous sinus thrombosis; Haemorrhagic infarction	CVST symptoms - 9 days	[redacted]
[redacted]	[redacted]	Chills, Acute respiratory failure, Headache, Gait disturbance, Pain in extremity, Dizziness, Vomiting, Cerebral venous sinus	9 days	Fatal. [redacted]

		thrombosis, Hemiparesis, Thrombocytopenia, Coordination abnormal, Pyrexia, Seizure		[redacted]

4. Discussion

For completeness, the evaluation has included cases of all thromboembolic events occurring with thrombocytopenia. The cases mainly involved individuals with cerebral venous thrombosis, although in a minority other venous system area and 1 case with arterial thrombus were also involved.

The pattern with age has attenuated slightly with older patients involved. In the cerebral venous thrombosis group, the majority at present still involve individuals under the age of 50, although this now includes individuals in the 60s- 70s. With non-cerebral thromboses, individuals were largely in their 60's – 70's. The events reported for CVTs affected both genders, while where gender was known the non-cerebral thromboses were mainly female . This is a slightly different clinical picture from cases seen in the EU which affected mostly women under 50.

A significant challenge with evaluation of this case series is that despite proactive attempts at follow-up, critical information on the cases remains significantly lacking. For this reason, a significant proportion of cases (18/28) were considered to be in the "Unclassified" category for assessment according to the WHO UMC case causality assessment (Event or laboratory test abnormality, more data for proper assessment needed). Information was unavailable in a majority of cases for risk factors for thrombotic events and thrombocytopenia. Of note alternative diagnoses were considered for three cases, including a [redacted] Additionally, 4 cases also had potential risk factors, at least for thromboses, these were inflammatory bowel disease with 5-ASA use, anorexia nervosa, fibromyalgia and immobility directly preceding the thrombotic event. There were also several cases where the individuals were on concomitant medication associated with thrombocytopenia.

No clear pattern of underlying mechanism was evident from the information received. Testing for "HIT" was reported as being performed in 4 cases, 1 of which was positive for anti-PF4 antibodies. Apart from one which mentions use of the Acustar system for testing, the cases do not specify the diagnostic assay used, which may lead to differences in sensitivity of detecting anti-PF4 antibodies. DIC was also considered in 1 case, although the rationale behind this was unclear given most other coagulation parameters were within normal range.

Information on response to treatment was also lacking, and no distinct pattern of response could be identified from the limited data available. Platelet transfusions were given in 5 patients, [redacted]

In one patient there appeared to be [redacted] although it is unclear if this truly preceded the events or if the reported intended to indicate this was used as treatment. 5 cases

describe use of low molecular weight heparin and 1 of IV heparin as treatment for the thrombotic event. In 1 case the patient was reported as recovering and 2 as stable. It is difficult to be definitive on whether the heparin in these cases may have caused thrombocytopenia, although in these cases the heparin does not seem to have caused clinical deterioration. Heparin was changed to argatroban in one case, the reason for this is not given.

There were 15 non-UK cases which the MHRA has case details on, 14 of these were from EU member states. Ages were largely <50 years with only one case in a [redacted] These occurred mostly in females, with 2 cases in males. Time to onset was between 4-14 days. 12 of the 15 cases concerned CVSTs, with 1 portal vein thrombosis and 2 ischaemic strokes. 8 patients reported potential confounding factors (contraception, Factor V leiden/ cardiolipin). As with the UK cases, data was incomplete or missing in many cases with regard to risk factors.

Although there is limited recourse to identifying a background rate for CVSTs + thrombocytopenia, the current reporting rate does not exceed the known background frequency of CVSTs occurring without thrombocytopenia previously stated in the previous paper of 5- 16/ million annually (Coutinho, 2012, Desavayagam, 2016). However, available information on the background rate of CVSTs occurring with thrombocytopenia is lacking.

COVID-19 status

An important factor considered was COVID-19 status, either prior or current. Both thrombocytopenia and thromboses have been noted to occur in the context of COVID-19 infection.

Only 1 patient was reported as being SARS CoV2 antibody positive, another reported no microbiological evidence of past COVID-infection. Of the cerebral thromboses cases there were 3 negative PCR and 1 negative lateral flow test and there was very limited information about prior or current COVID-19 infection amongst the non-cerebral thromboses. Information was missing in most cases reported, both amongst EU and global cases. Information was also largely missing amongst non-UK cases, with only 3 patients described as SARS-COV-2 negative.

A national multicentre retrospective study conducted in China revealed that the incidence of thrombocytopenia (< 150 * 109/L) on admission for COVID-19 infection was 36.2% (Liao et al 2020) which is similar to that in SARS (40–45%%) and MERS (36%).

Thromboembolic complications of COVID-19 are known to be common with some studies reporting rates in the range of 20-30% while others have reported rates as high as 40-70%. A meta-analysis by Malas et al (2020) found overall venous TE rate to be 21% (95% CI:17–26%), ICU, 31% (95% CI: 23–39%). These tend to correlate with more severe disease and death. Potential mechanisms such as elevated platelet activation, including platelet aggregation, platelet spreading, α granule secretion and dense granule release, among others are thought to be linked to thrombosis in COVID-19 (Zhang 2020).

Importantly, COVID-19 related thromboses can occur even after recovery from acute infection. In a case series of patients in Brazil, even in some cases with seemingly mild infection not requiring hospital treatment, patients developed thrombotic events 2 to 4 weeks following recovery (Vechi, 2020).

It is possible that at least in the younger cases, COVID-19 may have been milder/ asymptomatic and routine questioning to detect potential infection via past symptoms may not have been sufficiently sensitive to detect the event.

VTE and platelet consumption

A potential rationale raised is the occurrence of platelet consumption in the process of formation of an extensive clot, due to consumption of platelets on the surface, in a process akin to DIC, with potential further falls in platelet count in the first 24 to 36 hours (Kitchens). This would most likely be related to a moderate drop in platelet count (30-100 x 10^9) and there is insufficient detail from the cases presented to ascertain the trend of thrombocytopenia or if the thromboses preceded thrombocytopenia.

Possible mechanisms

Adenoviral vectored vaccines enter endothelial cells after intramuscular injection (Coughlan 2020). Thrombocytopenia has been reported after the intravenous administration of large doses of non-replicating adenoviral vectors used in gene therapy (Othman et al. 2007). Transient reductions in platelet counts were noted in a phase 1 study of a chimpanzee adenovirus type-3 vectored Ebola vaccine although no clinically significant thrombocytopenia was observed in the phase 2 study (Tapia et al. 2020). Intravenous dosing of non-replicating adenoviruses caused accelerated platelet clearance and activation of endothelial cells and platelets in animal studies (Othman et al. 2007, Wolins et al. 2003).

5. Case definition

At present a case definition is unclear based on the available data however based on some available information this might include:

- Any venous or arterial thrombosis AND
- Platelet count <150 x 10^9/L

Additional advice is sought on other criteria that can be added to the case definition, including time to onset, diagnostic criteria or additional risk factors.

In addition, MHRA has worked with experts on a proforma to gather further relevant details, this is circulated separately. The proforma aims to gather further clinical information on identified cases to ascertain other risk factors.

6. Conclusions

The evaluation of cerebral venous sinus thrombosis events occurring in conjunction with thrombocytopenia remains challenging based on data from spontaneous reporting alone. The incidence of CVST occurring with thrombocytopenia continues to be extremely rare. This rate (approximately 2.2 per million) currently does not exceed the background incidence for CVST alone of 5- 16/ million per year. Variable amount information is reported via spontaneous reports and critical data missing in many of the cases includes information on prior or current COVID-19 infection, information on concurrent risk factors for thrombocytopenia and thrombotic events and concurrent medication.

Although underreporting is always a possibility with spontaneous reporting systems, the recent statements by the MHRA and EMA may have raised awareness of the issue, likely resulting in the recent increase of cases.

Further data is needed to fully characterise this event, including on individuals potentially at risk, diagnostic criteria, potential other associated sites of thromboses and treatment options.

7. Advice sought from the EWG

1. Does the EWG consider there to be sufficient evidence of an association between COVID-19 vaccine AstraZeneca and cerebral venous thromboses occurring with thrombocytopenia?
2. Does the EWG consider there to be sufficient evidence of an association between COVID-19 vaccine Astra Zeneca and other thromboses occurring with thrombocytopenia?
3. Could the EWG advise on further criteria to be included in the case definition?
4. Does the EWG agree use of the current proforma, or could the EWG advise on any additional items to include?

References

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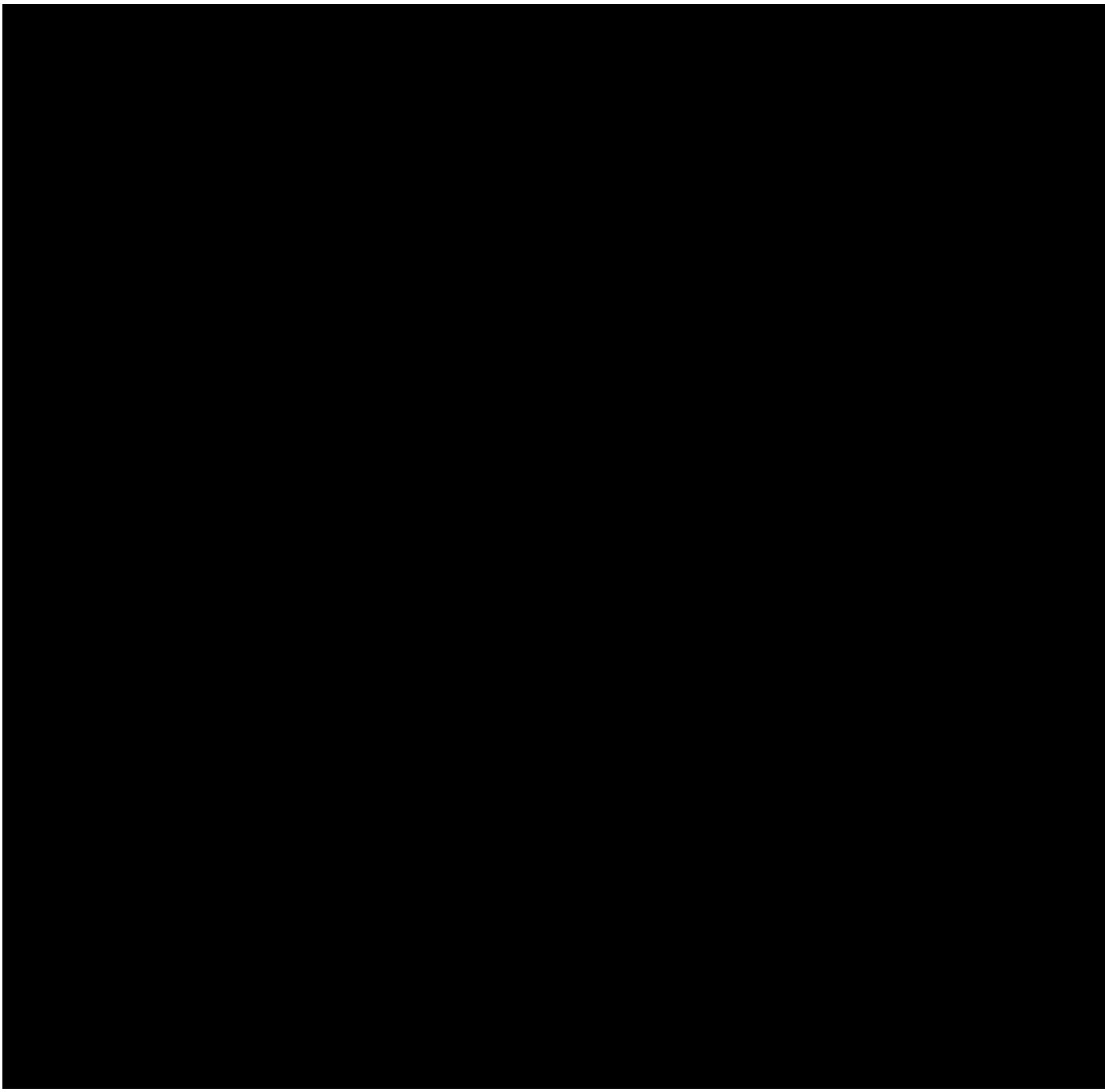
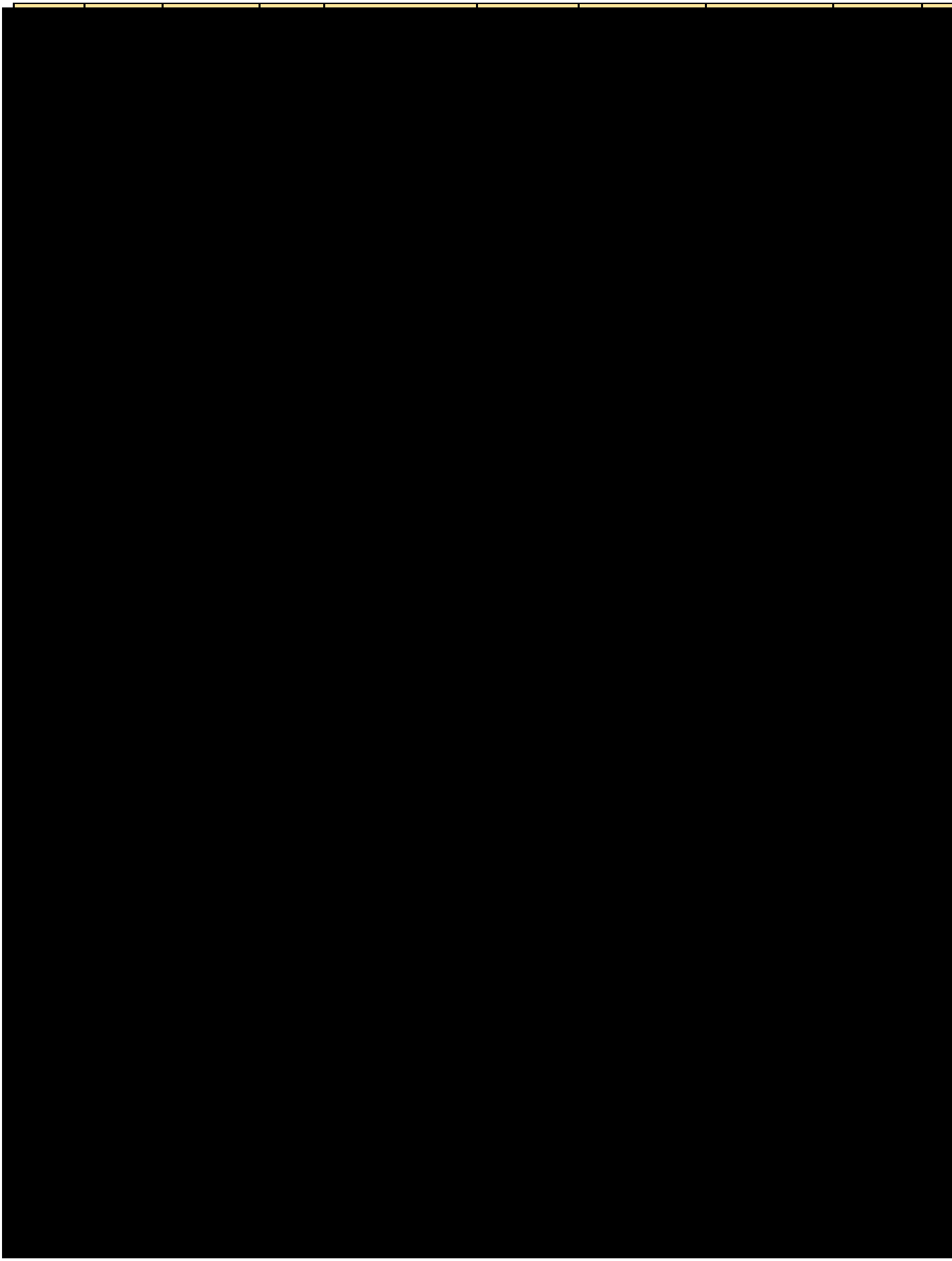
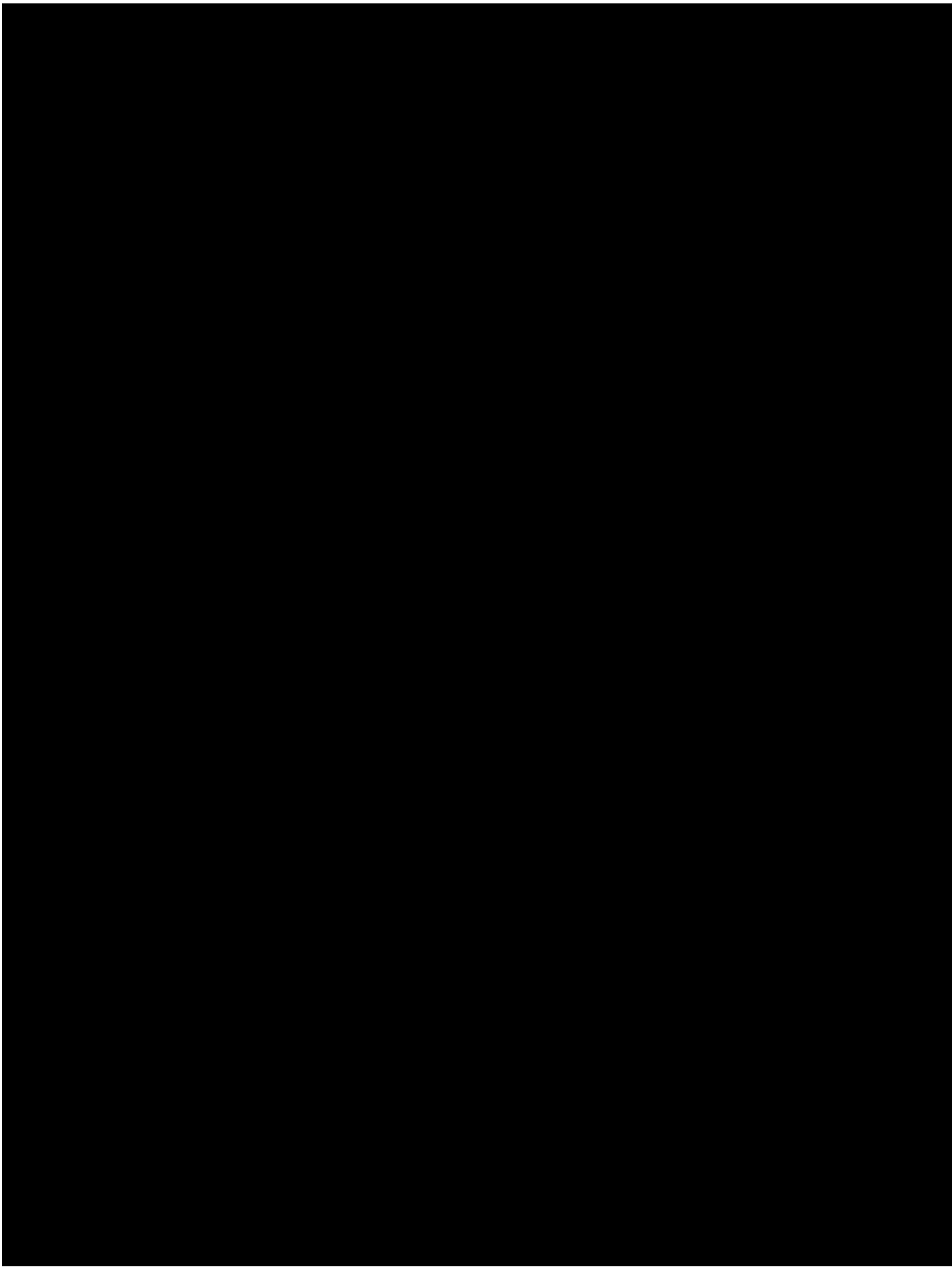
Annex 1 Tabulation of cases of thromboembolic events with thrombocytopenia reported to MHRA up to 21/03/2021

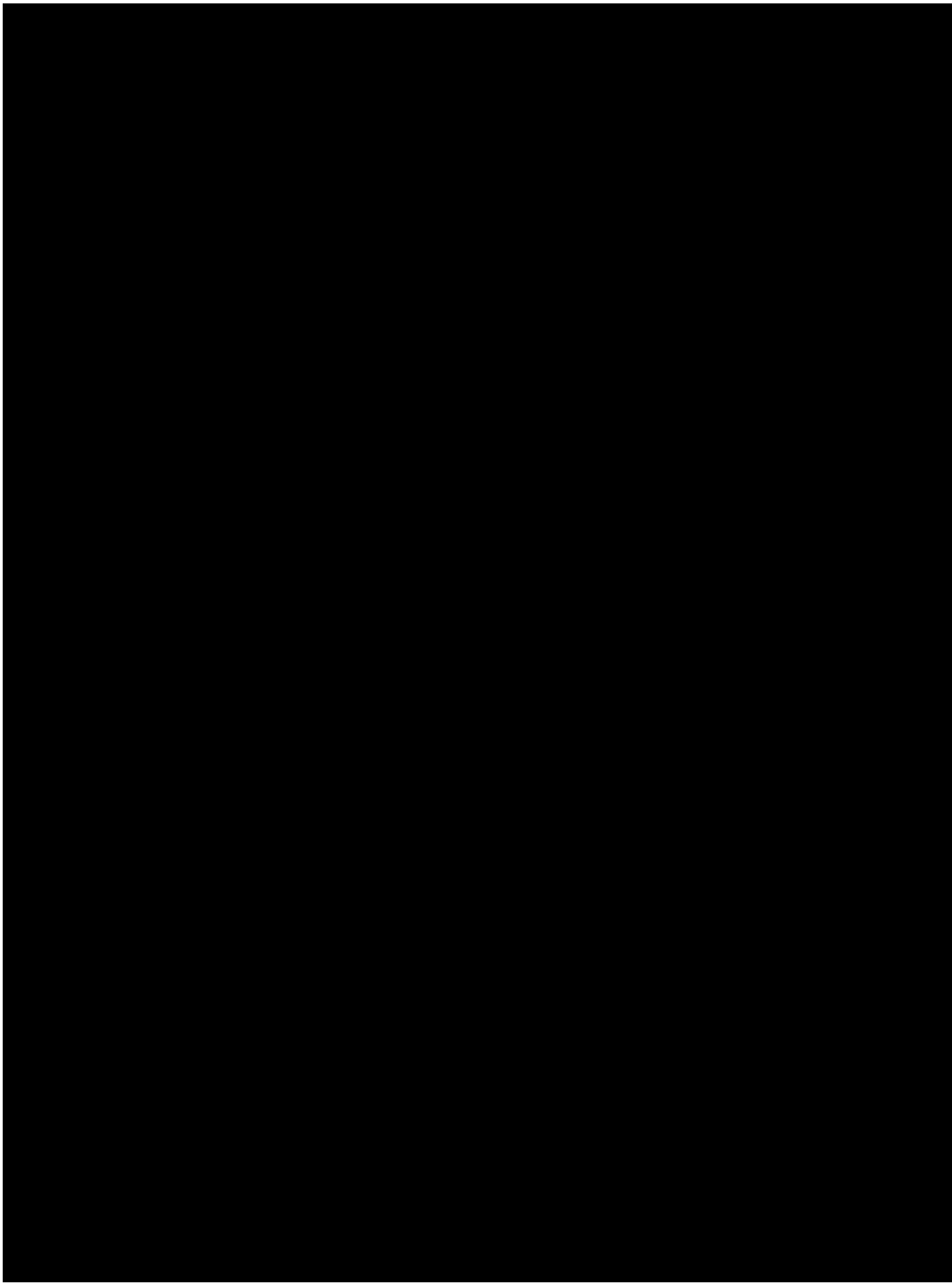
Tabulation of cases of thromboembolic events with thrombocytopenia reported to MHRA up to 21/03/2021

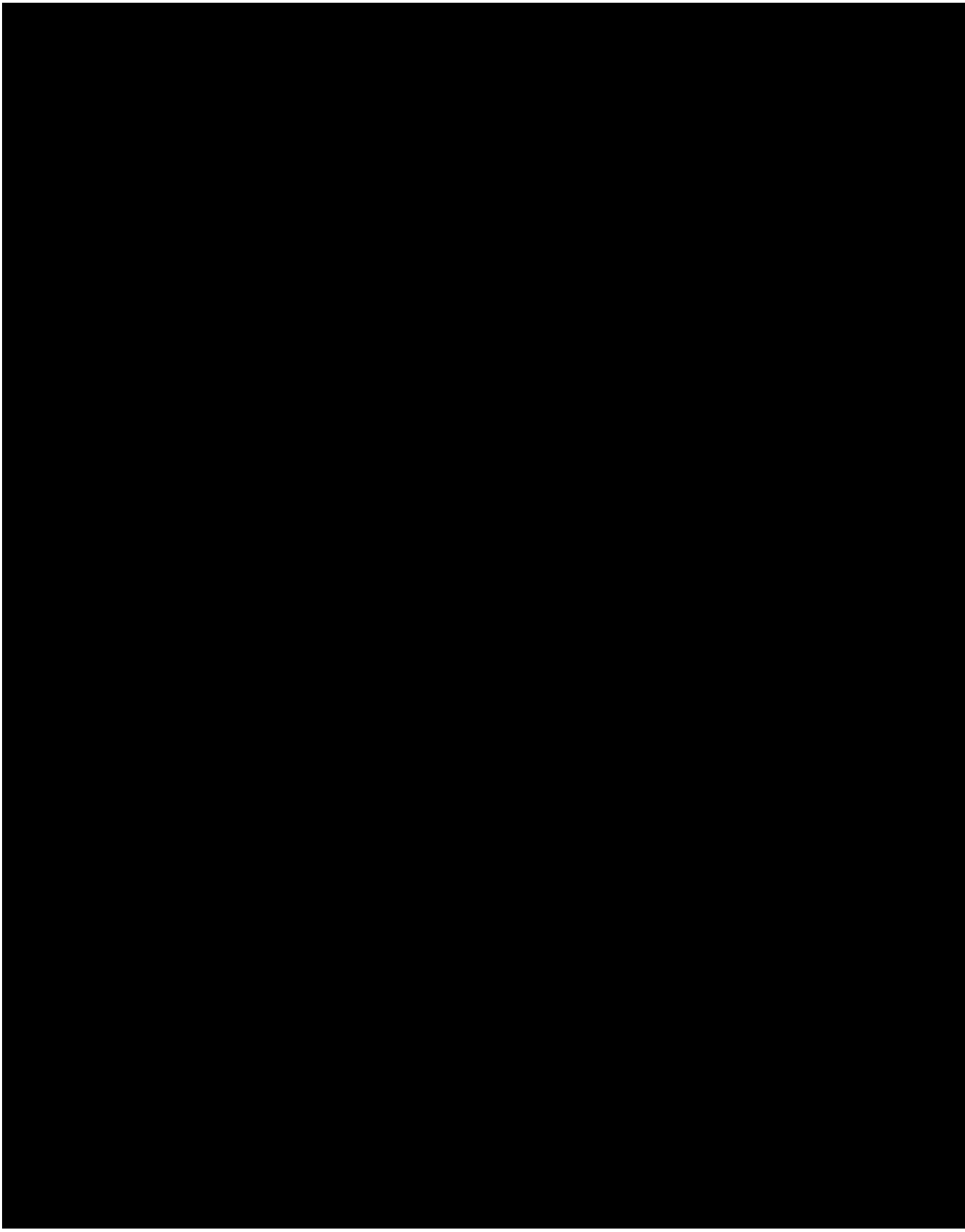
Cases reporting a cerebral venous sinus thrombosis are highlighted in yellow
Cases reporting other types of thrombosis are highlighted in green

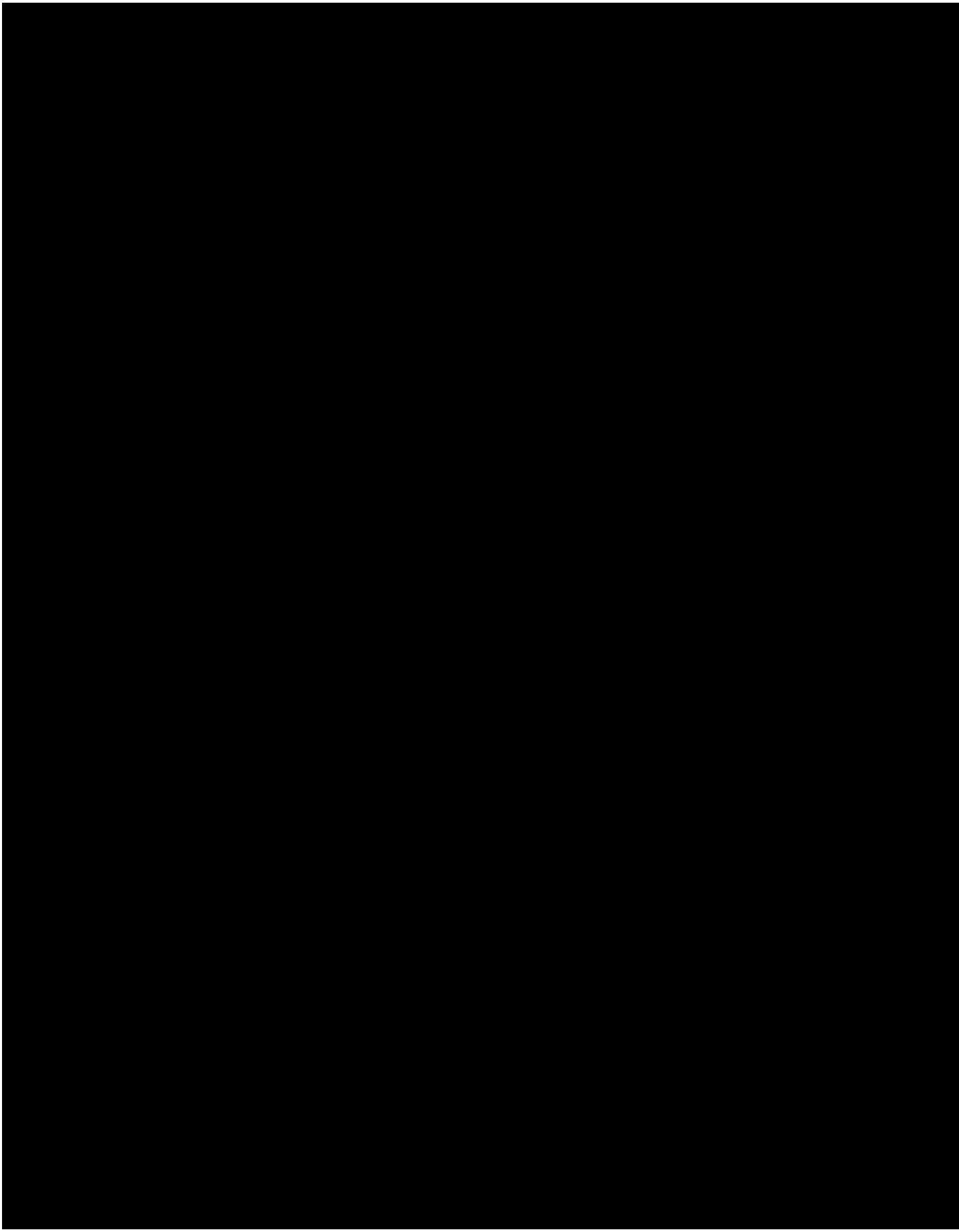


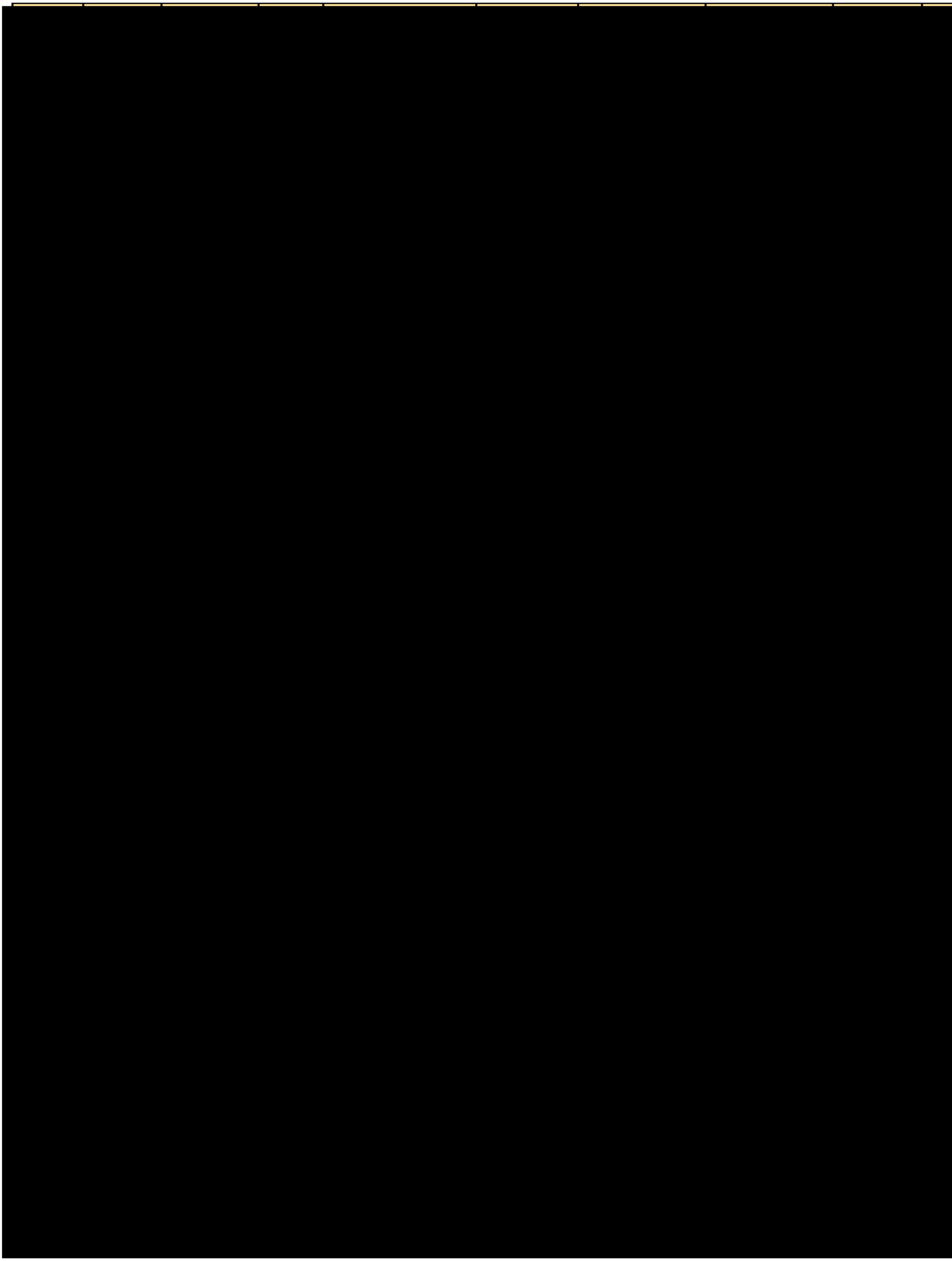


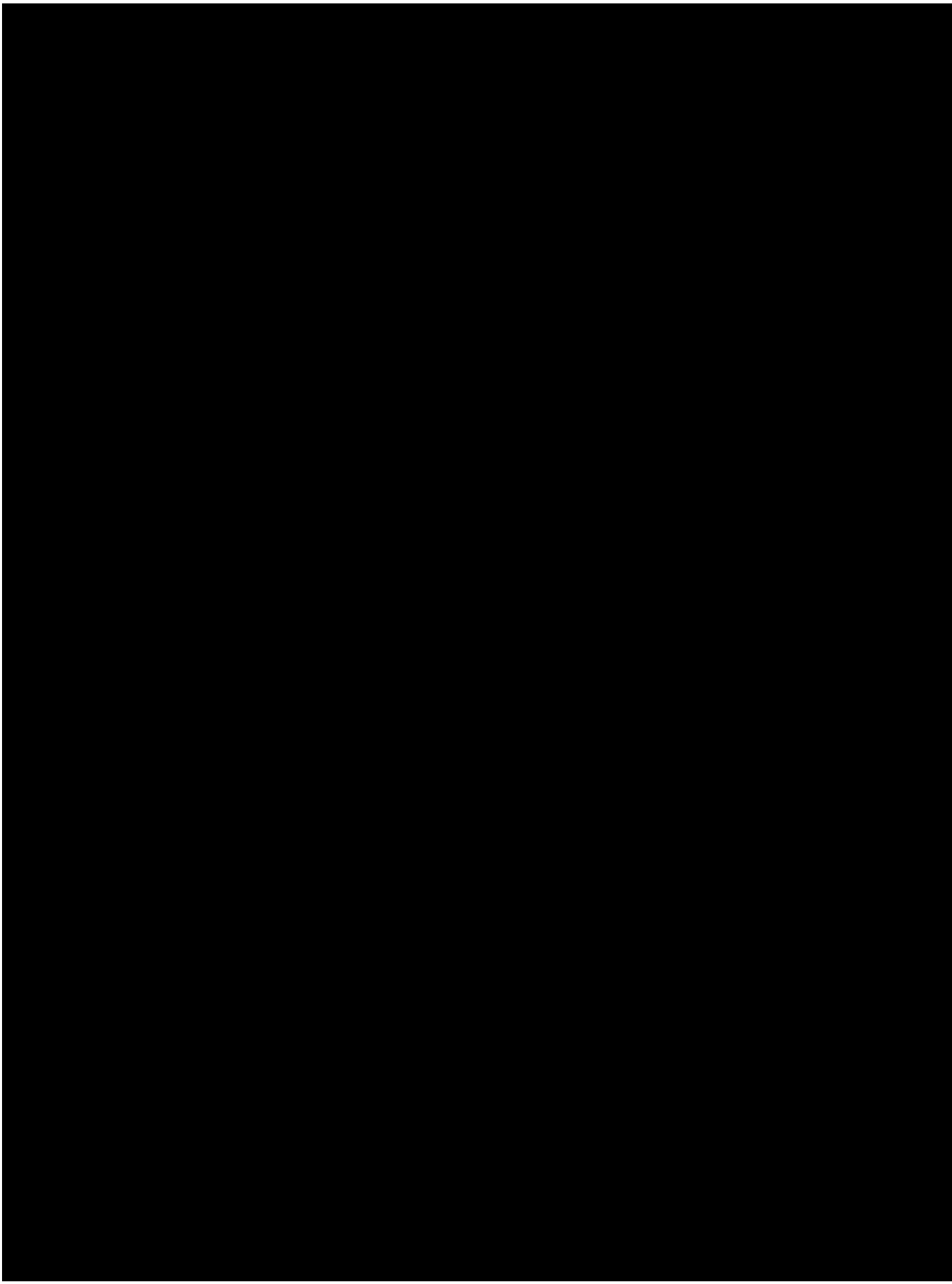


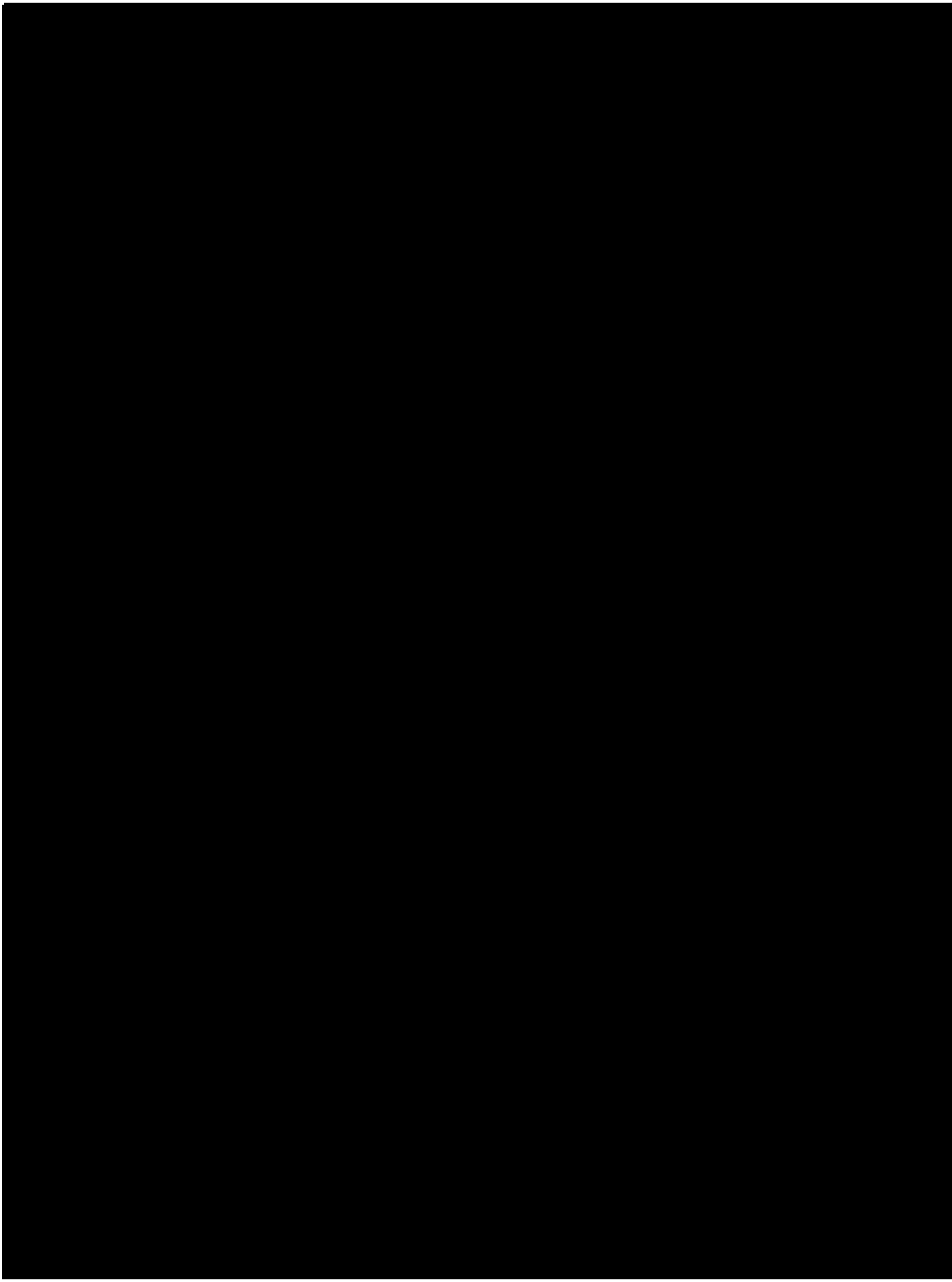


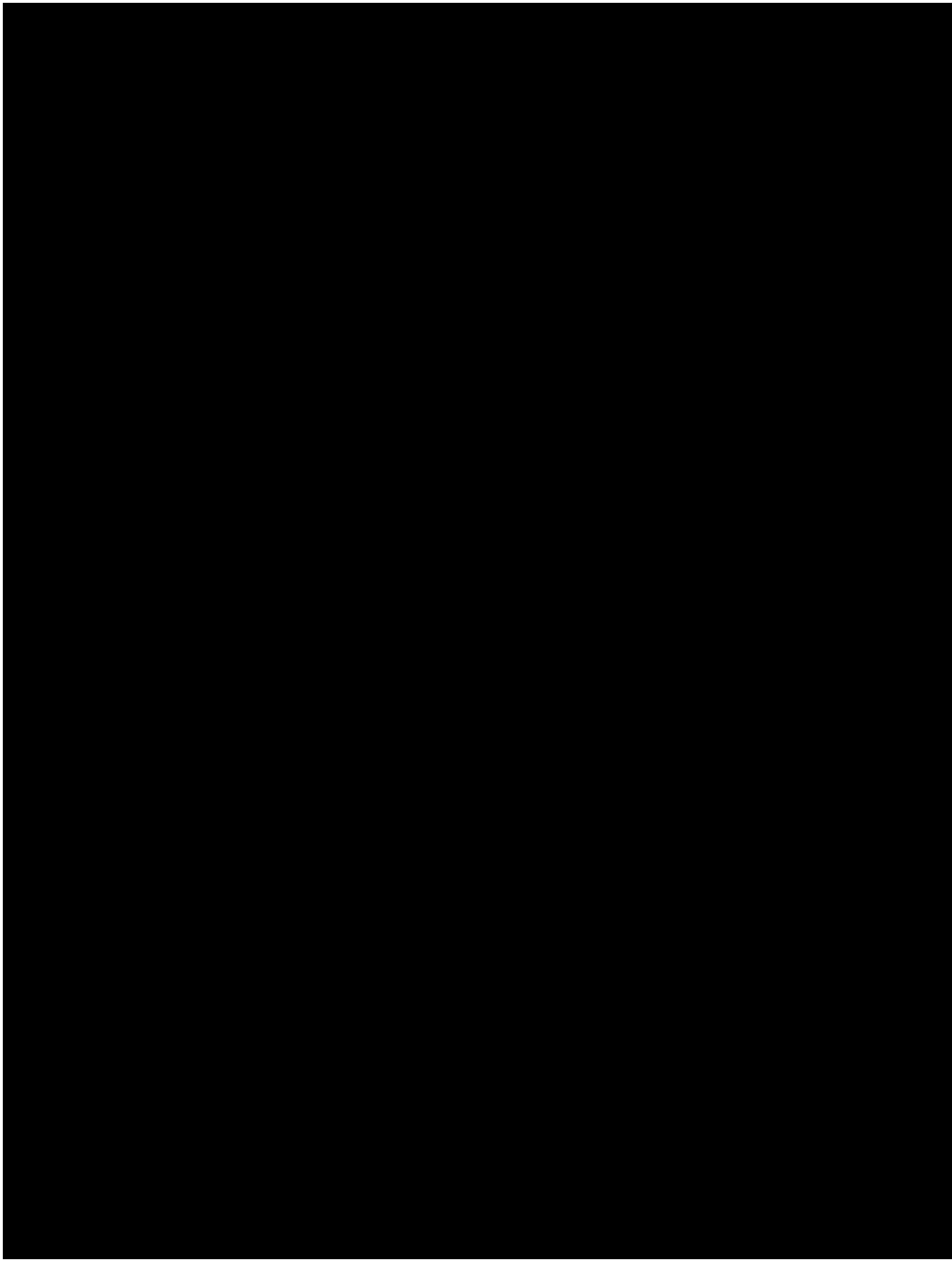


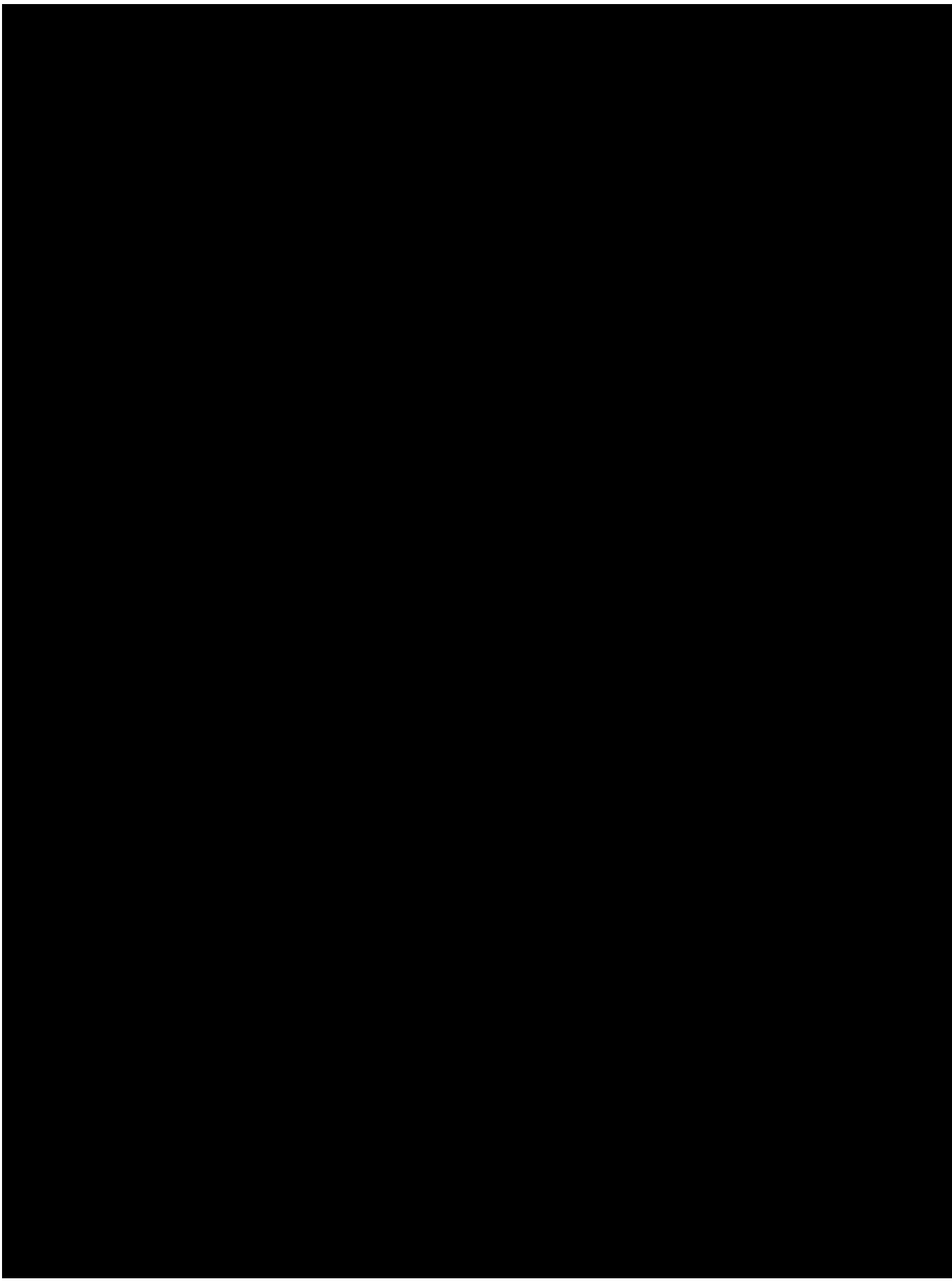












[redacted]

[i]This includes alternative diagnoses for:

- Thrombocytopenia: infectious causes (including SARS-CoV-2, HIV, hepatitis C, hepatitis B, herpes zoster, cytomegalovirus), malignancy including metastatic disease, leukaemia, myelofibrosis, lymphoproliferative disorders, thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation(DIC), heparin induced thrombocytopenia and thrombotic syndrome (HITT), autoimmune/ inflammatory disease eg: systemic lupus erythematosus (SLE), antiphospholipid syndrome, medications with thrombocytopenic effect
- Thrombosis: active malignancy (incl. intracranial), infection (localised eg: meningitis, sinusitis, otitis or systemic), significant dehydration, immobility, previous venous thromboses, protein C and S deficiency, systemic inflammatory/ autoimmune diseases, acquired prothrombotic states (including nephrotic syndrome), pregnancy/ puerperium, Factor V Leiden mutation, antiphospholipid syndrome, hyperhomocysteinaemia, sickle cell disease, haematological disorders, oral contraception, antithrombin deficiency, surgical procedures/ medical interventions to the central nervous system (surgery/ lumbar puncture)

Table produced by [redacted] and [redacted] **Annex 2. Tabulation of non-UK cases of thromboembolic events with thrombocytopenia**

The cases in the table below comprise of the following 21 case reported from outside the UK (1 case from [redacted] and 20 EU cases):

- **8 cases identified by AstraZeneca of thrombocytopenia with co-reported embolic and thrombotic events comprising of the following cases:**
  - 5 non-UK cases identified as of 13 March 2021 from Austria (2 reports), [redacted] (1 report), [redacted] 1 report), [redacted] (1 report). *Nb. 2 UK cases were also identified by AstraZeneca up to 13/3/21 and are presented in the table in Annex 1.*
  - 3 additional cases identified by AstraZeneca as of 16 March of thrombocytopenia with a co-reported event identified from the SMQ of embolic and thrombotic events from Greece (2 reports) and [redacted] (1 report)

- *Nb. AstraZeneca also identified 2 additional reports, one report from* [redacted] *and one report from* [redacted] *These cases are not included in the table below as a thrombotic event was not co-reported in these cases*.

- **13 additional EU cases reporting thrombosis and thrombocytopenia not identified in the search conducted by AstraZeneca comprising of the following cases:**

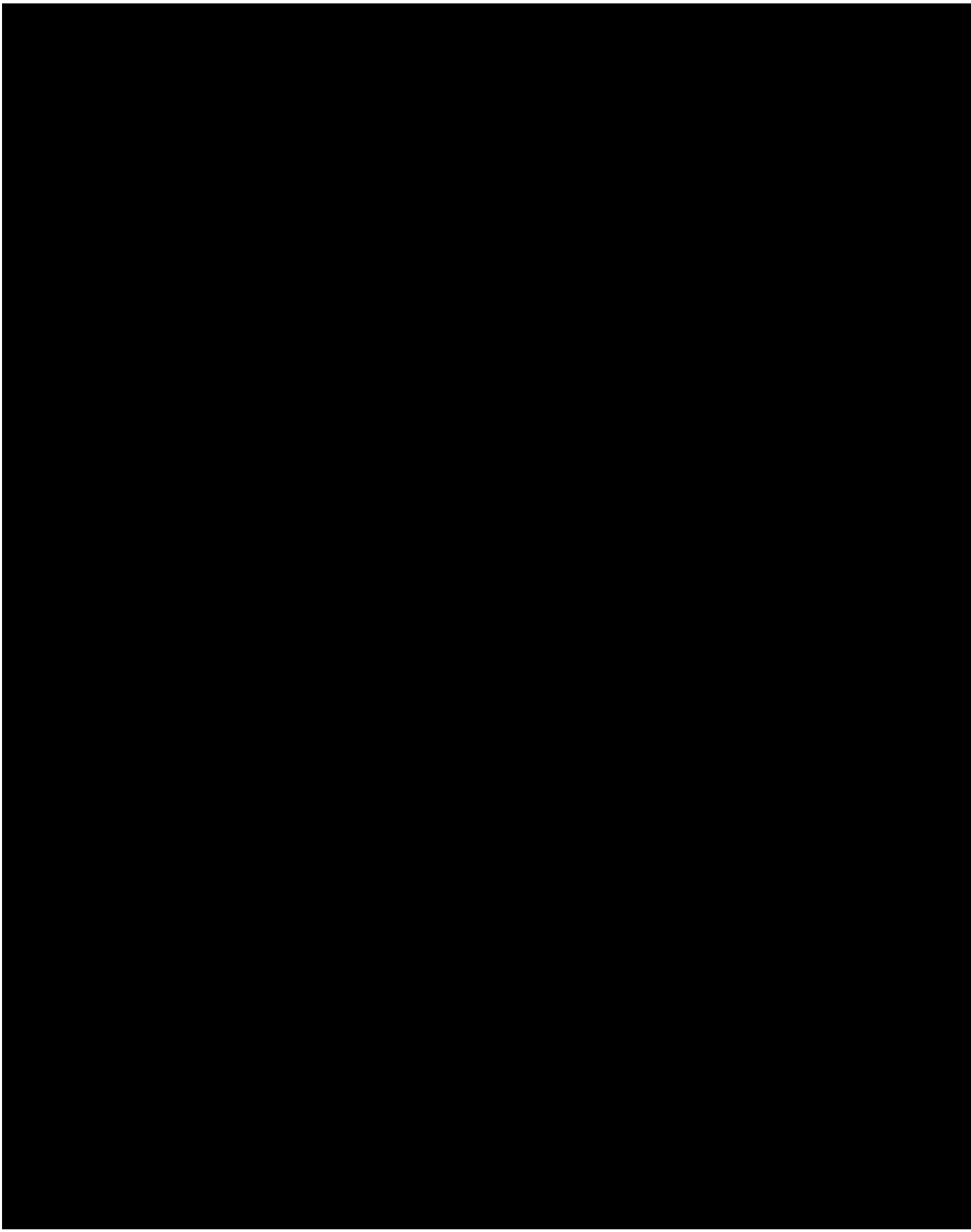
  - **Germany:** 7 cases of sinus thromboses and thrombocytopenia from Germany as of 16/03/2021; one case may be a possible duplicate of a case identified by AstraZeneca

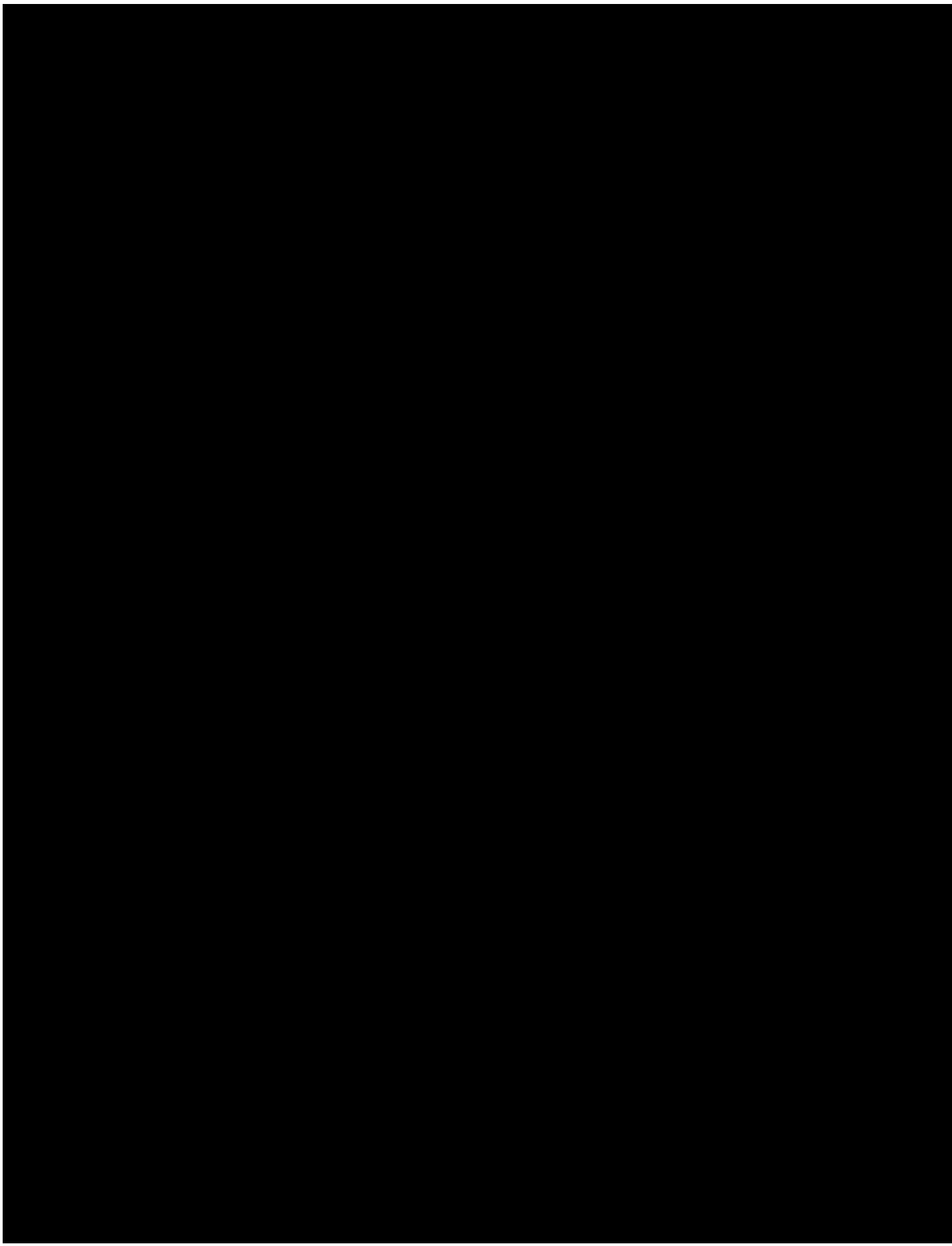
  - [redacted] One case of left sided paralysis, cerebral artery occlusion, ischemic cerebral infarction, thrombocytopenia, systemic hypercoagulative disorder and disseminated intravascular coagulation f[redacted]

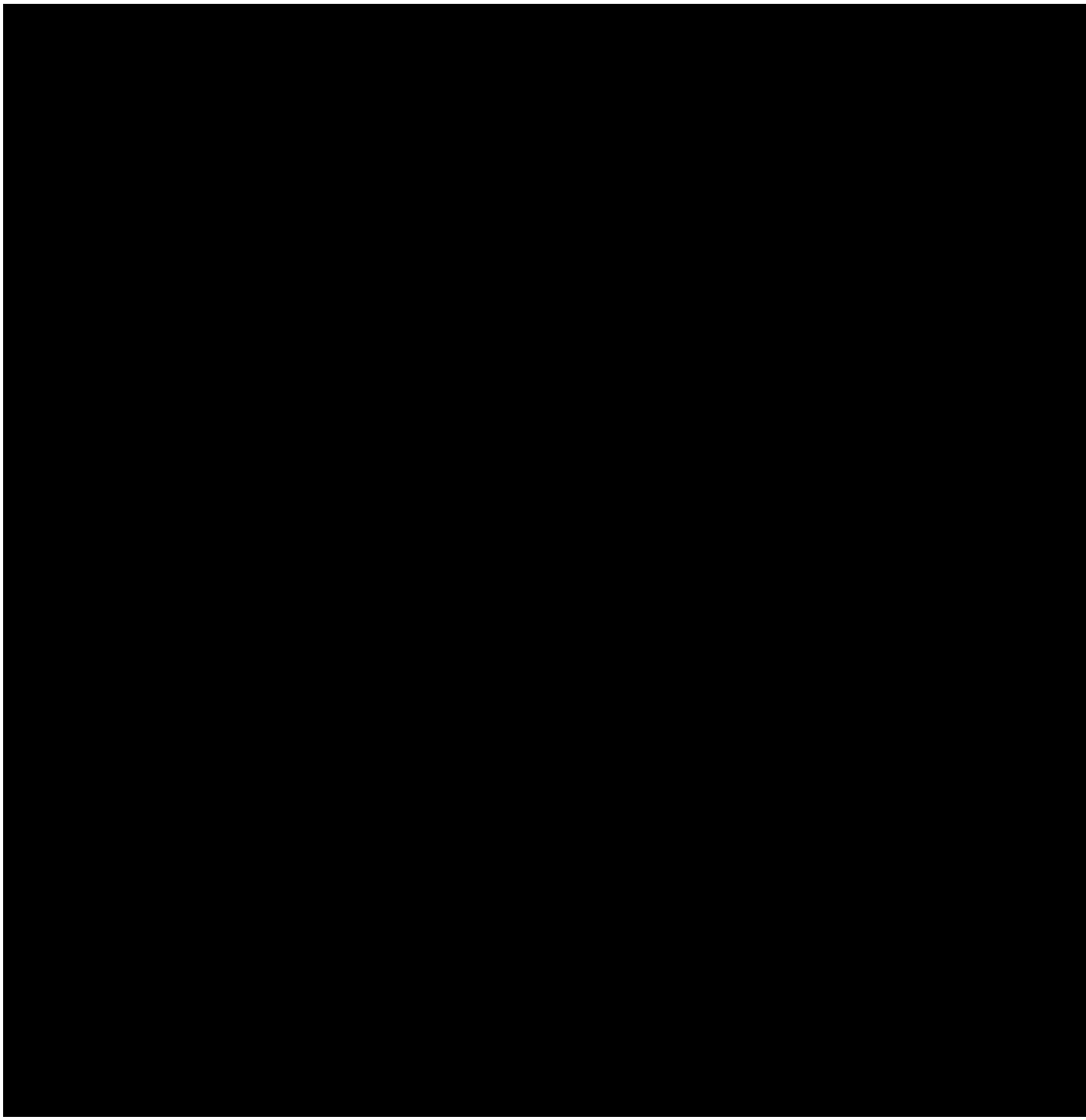
  - **Norway:** 5 cases of thrombus and thrombocytopenia from Norway received as of 16 March 2021

[redacted]

[redacted]







[i]This includes alternative diagnoses for:

- Thrombocytopenia: infectious causes (including SARS-CoV-2, HIV, hepatitis C, hepatitis B, herpes zoster, cytomegalovirus), malignancy including metastatic disease, leukaemia, myelofibrosis, lymphoproliferative disorders, thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation(DIC), heparin induced thrombocytopenia and thrombotic syndrome (HITT), autoimmune/ inflammatory disease eg: systemic lupus erythematosus (SLE), antiphospholipid syndrome, medications with thrombocytopenic effect
- Thrombosis: active malignancy (incl. intracranial), infection (localised eg: meningitis, sinusitis, otitis or systemic), significant dehydration, immobility, previous venous

thromboses, protein C and S deficiency, systemic inflammatory/ autoimmune diseases, acquired prothrombotic states (including nephrotic syndrome), pregnancy/ puerperium, Factor V Leiden mutation, antiphospholipid syndrome, hyperhomocysteinaemia, sickle cell disease, haematological disorders, oral contraception, antithrombin deficiency, surgical procedures/ medical interventions to the central nervous system (surgery/ lumbar puncture)