Section A: Clarification on effectiveness data

A1. **Priority request:** Please provide the WinBUGs working code for each outcome reported in the network meta-analysis in the submission (i.e. including the appropriate parameter data for priors and trials included in the analysis).

Please refer to the attachments - Attachment 1 and Attachment 2 + 3.

A2. **Priority request**: Please complete the following table to provide the results for each of the outcomes assessed in the network meta-analysis using the ROCKET-AF ITT data and the restricted set of comparators, i.e. odds ratios for rivaroxaban compared with selected comparators.

Please see below the results from the NMA for the ITT population from ROCKET AF. Results do not include the safety endpoints as the safety on-treatment summaries are the only relevant summaries for evaluation of safety events. Furthermore, the ITT population in ROCKET AF is not comparable with ITT in the other trials in the NMA due to the prolonged "off treatment" period - in the full ITT (to site notification), there was a median of 117 days of follow-up assigned medication i.e. patients were off randomised treatment.

In ROCKET AF, if non-inferiority was declared in the per protocol population, then superiority on the primary efficacy endpoint was then to be based on on-treatment data from the safety population.

	Adj dose warfarin		Acetylsalicylic Acid		Dabigatran 110mg		Dabigatran 150mg		Placebo	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Composite (ischaemic stroke & systemic embolism)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic stroke	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhagic stroke / ICH										
Systemic embolism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major haemorrhage										
Minor bleed										
Gastrointestinal bleed										
Transient ischaemic										

attack										

Please note that the odds ratios here presented should be interpreted in the following way: odds ratios greater than 1.0 mean that the event is less likely in the rivaroxaban group than in the comparators 'group, and vice-versa; odds ratios of 1.0 mean there is no difference between rivaroxaban and comparators.

A3. **Priority request**: Please complete the table below to provide details on the number of people in the ROCKET-AF trial who switched to open label warfarin in the ITT population (i.e. before site notification ITT population).

The following table represents the antithrombotic therapies received after the last dose of double-blind study medication in those patients who had "early study medication discontinuation".

	Rivaroxaban			**Warfarin**		
	n	**N**	~~**Event rate (100 pt year)**~~ **% of those patients with early study medication discontinuation**	**n**	**N**	~~**Event rate (100 pt year)**~~ **% of those patients with early study medication discontinuation**
Number of people who switched to open label VKA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number remaining on randomised blinded study drug	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other anticoagulants excluding VKA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Aspirin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thienopyridine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A4. **Priority request**: Please provide table 21 for the ITT and safety on treatment populations (% INR values in therapeutic range for warfarin by region).

Data from the safety population is provided in the original submission (Table 21).

Imputed INR is calculated for the safety population on treatment using Point of Care device measurements. It is useful only for patients taking warfarin and thus it would not make sense to use off treatment data from the ITT population. In addition, the Point of Care device was not used in the off-treatment period. Therefore we feel it is not appropriate or relevant to provide this data.

A5. **Priority request**: Please provide a rationale for why there were more major gastrointestinal bleeding events in the rivaroxaban group than in the warfarin group of ROCKET-AF (224 bleeds [3.15%] with rivaroxaban vs. 154 bleeds [2.16%] with warfarin).

At the current time, any rationale proposed regarding gastrointestinal bleeding events is speculation. It is important to consider that the rate of major bleeding was similar between rivaroxaban and warfarin groups and that the most critical bleeding events are significantly reduced with rivaroxaban (fatal bleeds and ICH).

The pattern of mucosal bleeding events identified within the rivaroxaban treatment group appears to demonstrate certain characteristics consistent with inherited factor X deficiency. This is a rare genetic disorder that follows an autosomal recessive hereditary transmission, occurring in about 1:1,000,000 subjects. Due to the rarity of the disease no large databases exist. However, case reports and several international registries provide a clinical phenotypic picture that varies with the kindred. Factor X coagulant activity levels above 20% are infrequently associated with bleeding, and heterozygotes are usually asymptomatic. The more severe inherited factor X deficiency patients commonly experience hemarthroses and hematomas, but gastrointestinal bleeding, hematuria, and CNS bleedings may also occur. The more moderately affected may experience a preponderance of muco-cutaneous bleeding events of easy bruising, epistaxis, and gum bleeding, as well as gastro-intestinal bleeding events and hematuria rather than intracranial hemorrhage and enclosed organ bleeding events (e.g., those captured by the "critical organ bleeding" endpoint in ROCKET AF).

Thus, from the literature it can be concluded that the bleeding pattern seen with treatment of patients with the Factor Xa inhibitor rivaroxaban, with the observed predilection for bleeding from mucosal sources, corresponds to the bleeding pattern seen in patients with mild or moderate inherited factor X deficiency. Like any anticoagulant drug, rivaroxaban also has the potential of unmasking occult pre-existing anatomic or pathologic lesions which may have been causing occasional or intermittent subclinical blood loss prior to becoming clinically evident (macroscopic or symptomatic) once a potent anticoagulant has been administered.

It may be reassuring to note that major bleeding with blood transfusion ≥ 4 units while in the safety on treatment population occurred in the same number of patients in the rivaroxaban and warfarin arms - see table below.

	Rivaroxaban N = 395 n (rate)	Warfarin N = 386 n (rate)	Rivaroxaban vs warfarin HR (95% CI)
Total number of subjects receiving transfusion ≥ 4 units for a major bleeding event	64 (0.57)	64 (0.57)	1.01 (0.72, 1.43)

N = number of subjects with major bleeding events
Rate = number of events per 100 patients-years

In addition, the following results also show that fatal GI bleedings are numerically in favour of rivaroxaban (1 compared to 5).

Bleeding site	Rivaroxaban n/N (%)	Warfarin n/N (%)
Total number of subjects with major bleeding events with fatal outcome	27/395 (6.84)	55/386 (14.25)

Intracranial	24/55 (43.64)	42/84 (50)
Gastrointestinal - upper	1/151 (0.66)	3/104 (2.88)
Gastrointestinal – lower	0/49	2/32 (6.25)
Other	2/151 (1.32)	8/181 (4.42)

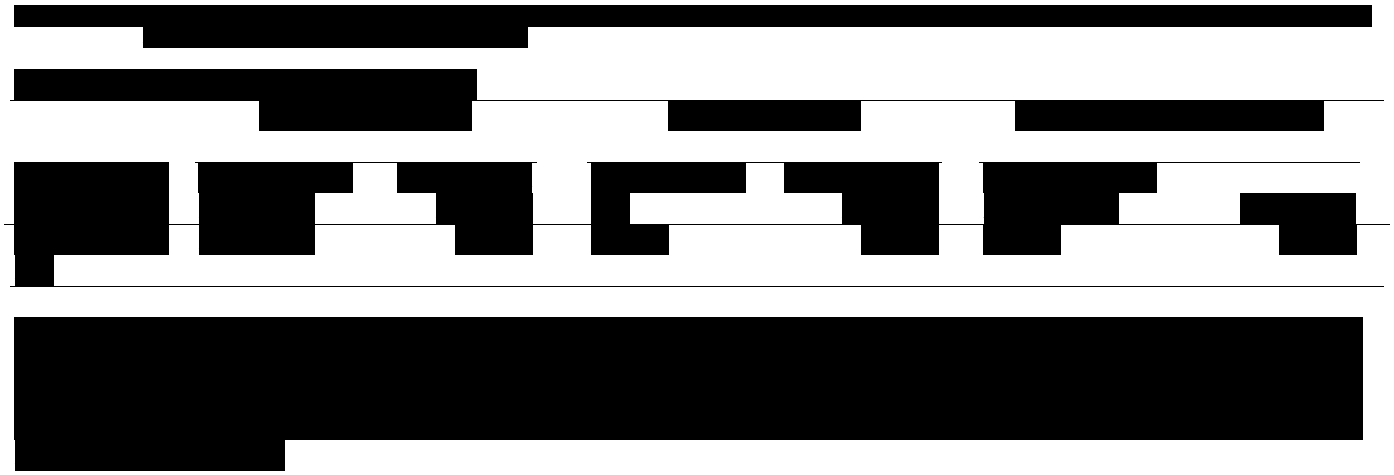
n = subjects who died
N = number of subjects with major bleeding site

A6. **Priority request**: Please complete the table below to provide details on the rates of dyspepsia in the rivaroxaban and warfarin groups of ROCKET-AF.

This table will be provided for safety on-treatment only. This is the most relevant population for description of adverse effects of treatment and was the pre-planned primary analysis population for safety events.

Bayer assumes that this request is due to dyspepsia being raised within the recent NICE appraisal of dabigatran in this indication. Whilst dyspepsia is an adverse event associated with dabigatran, it is not an adverse effect of note in the ROCKET AF trial. The manufacturer's submission for dabigatran states *"The only other adverse event that was significantly more common with DBG than with WFN was dyspepsia or gastritis-like symptoms (including abdominal discomfort)."*

When the table of the 15 most frequent treatment-emergent adverse events based on the rivaroxaban treatment group in the ROCKET AF trial is examined, dyspepsia is not listed *[Supplement to: Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011. DOI: 10.1056/NEJMoa1009638.]*



A7. **Priority request**: Please provide a PRISMA flow diagram for the network meta-analysis and explain any discrepancies in numbers between the PRISMA diagram and the details provided in the Oxford Outcomes systematic review and network meta-analysis reports provided with the submission.

Apologies for the discrepancies noted. The original PRISMA flow diagram in the systematic review report cited 33 studies reported over 53 publications. Following a search update in February 2011 the relevant numbers of studies and publications in the qualitative review were 35 and 55. (See Figure below)

These 35 studies included Pengo (2010) and RE-LY (2009) not covered by the original search. Seven studies (14 publications) included in the original 33 qualitatively reviewed were excluded from the network meta-analysis, resulting in there being 28 studies identified by the systematic review retained in the network meta-analysis. (See table below)

In addition two studies whose results were not published at the time of the latest searches were also included in the network meta-analyses. These studies were AVERROES, published shortly after the searches were updated, and ROCKET.

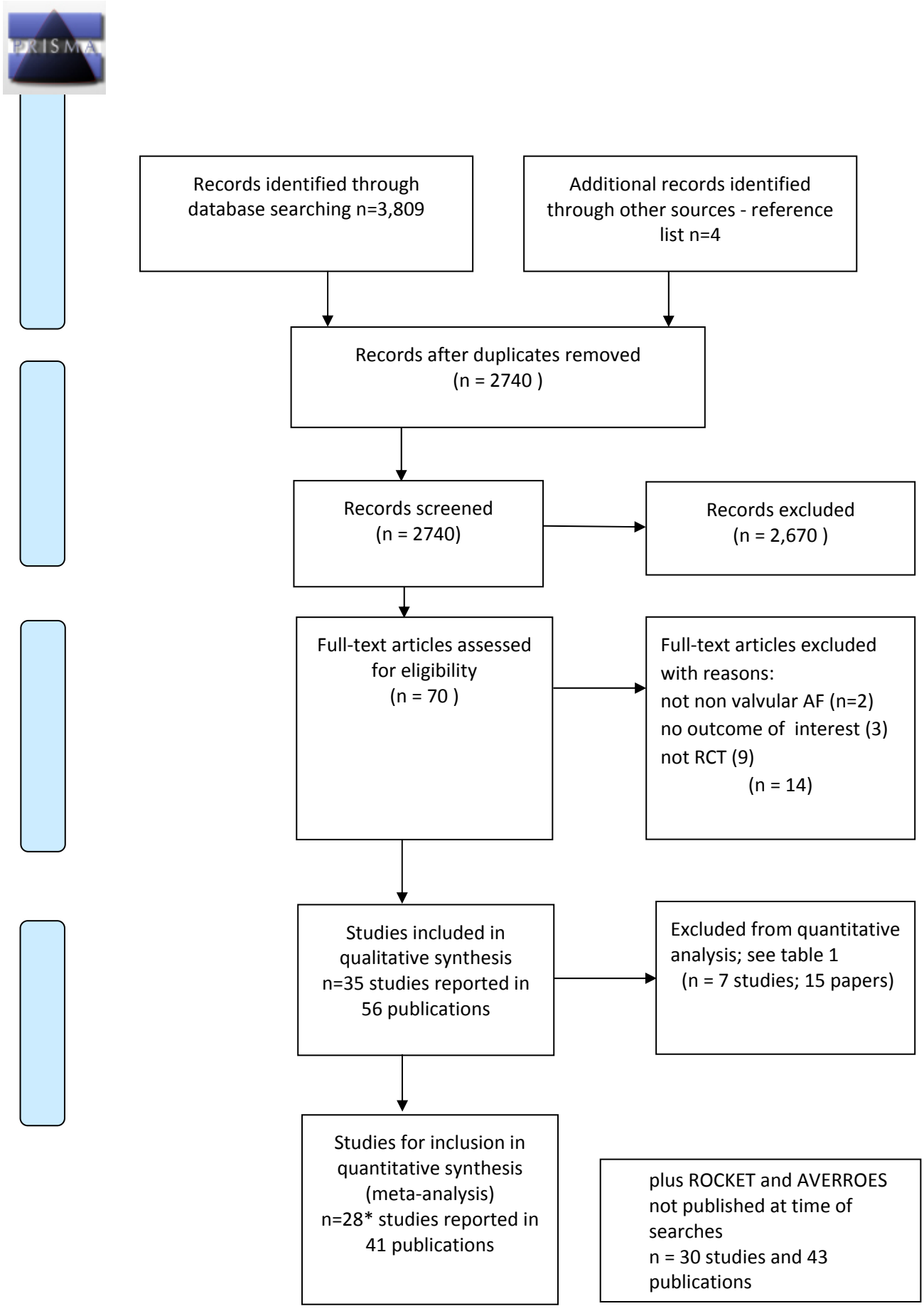
Thus a total of 30 studies were included in the network meta-analyses. These cover all comparators identified by the review (including e.g. fixed low-dose warfarin that may be of little relevance). Analyses for individual endpoints are based on the availability of data in the individual studies.

Table Studies in qualitative review excluded from network meta-analysis

STUDY	REASON EXCLUDED FROM NMA
CHARISMA	Of 15,603 (patients > 45 years with either clinically evident cardiovascular disease or multiple risk factors), 583 (4%) were AF patients. AF sub-group results inadequately reported for NMA.
ESPS-II	Of 6,602 patients who had had experienced a cerebrovascular event 429 (6.5%) were AF patients. AF sub-group results inadequately reported for NMA.
ESTEEM	Of 1,883 patients with MI 174 (9%) were AF patients. AF sub-group results inadequately reported for NMA.
Hu et al	Chinese language publication
Lu et al	Chinese language publication
SPAF I	SPAF II is an extension study of SPAF I. Inclusion of both studies within the NMA would result in double counting of clinical events.
SPORTIF II	Dose ranging study (n=254 in 4 arms) of ximelagatran in combination with aspirin

The Chinese publications excluded following receipt of translations which suggested the studies were of small numbers of patients with uncertain reporting.

Figure Revised Flow Diagram



References for studies included in qualitative review and/or network meta-analysis

Studies excluded from the network meta-analysis are shaded grey

Reference list includes ROCKET and AVERROES studies for which results were not yet published at time of searches.

ACTIVE A	Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, et al; The Active Steering Committee. Effect of clopidogrel added to aspirin in patients with atrial fibrillation . New England Journal of Medicine 2009 May 14;360(20):2066-78.
ACTIVE W	Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, et al; ACTIVE Writing Group of the ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial . Lancet 2006 Jun 10;367(9526):1903-12.
ACTIVE (design paper)	Connolly S, Yusuf S, Budaj A, Camm J, et al; The Active Steering Committee. Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. American Heart Journal 2006 Jun;151(6):1187-93.
AFASAK I	Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. Lancet 1989 Jan 28;1(8631):175-9.
AFASAK II	Koefoed BG, Gullov AL, Petersen P. Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulant Therapy Study (AFASAK 2): Methods and Design. J Thromb Thrombolysis 1995;2(2):125-30.
	Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study . Archives of Internal Medicine 1998 Jul 27;158(14):1513-21.
AMADEUS	Amadeus I, Bousser MG, Bouthier J, Buller HR, Cohen AT, Crijns H, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial . Lancet 2008 Jan 26;371(9609):315-21.
AVERROES (not in SR)	Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011 Mar 3;364(9):806-17.
BAATAF	The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators . New England Journal of Medicine 1990 Nov 29;323(22):1505-11.
BAFTA	Mant JW, Richards SH, Hobbs FD, Fitzmaurice D, Lip GY, Murray E, et al. Protocol for Birmingham Atrial Fibrillation Treatment of the Aged study (BAFTA): a randomised controlled trial of warfarin versus aspirin for stroke prevention in the management of atrial fibrillation in an elderly primary care population [ISRCTN89345269]. BMC Cardiovascular Disorders 2003 Aug 26;3:9.
	Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial . Lancet 2007 Aug 11;370(9586):493-503.
	Mant J, Hobbs R, Fletcher K, Roalfe A. Is warfarin a safe alternative to aspirin in elderly patients with atrial fibrillation? 205. Cardiology Review 25(7)()(pp 32-36), 2008 Date of Publication: July 2008 2008;(7):32-6.

CAFA	Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. Journal of the American College of Cardiology 1991 Aug;18(2):349-55.
CHARISMA (excl NMA)	Bhatt DL, Topol EJ. Clopidogrel added to aspirin versus aspirin alone in secondary prevention and high-risk primary prevention: rationale and design of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial. Am Heart J 2004 Aug;148(2):263-8.
	Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med 2006 Apr 20;354(16):1706-17.
	Hart RG, Bhatt DL, Hacke W, Fox KA, Hankey GJ, Berger PB, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of stroke in patients with a history of atrial fibrillation: subgroup analysis of the CHARISMA randomized trial. Cerebrovasc Dis 2008;25(4):344-7.
EAFT	Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group . Lancet 1993 Nov 20;342(8882):1255-62.
	van Latum JC. The 'European atrial fibrillation study': Secondary prevention of thromboembolic complications with oral anticoagulants or acetylsalicylic acid in patients with non-rheumatic atrial fibrillation. [Dutch]. Nederlands Tijdschrift voor Geneeskunde 138(20)()(pp 1025-1031), 1994 Date of Publication: 1994 1994;(20):1025-31.
ESPS II (excl NMA)	Bertrand-Hardy JM, Cunha L, Forbes C, Hoeven C, Hogenhuis L, Lowenthal A, et al. European Stroke Prevention Study 2: Baseline data. Journal of the Neurological Sciences 1995 Aug;131:Suppl-58.
	Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996 Nov;143(1-2):1-13.
	Diener HC, Lowenthal A. Reply to Dr G. Hart and Dr O. Benavente. Journal of Neurological Sciences 1997;153:112.
ESTEEM (excl NMA)	Wallentin L, Wilcox RG, Weaver WD, Emanuelsson H, Goodvin A, Nystrom P, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet 2003 Sep 6;362(9386):789-97.
	Tangelder MJ, Frison L, Weaver D, Wilcox RG, Bylock A, Emanuelsson H, et al. Effect of ximelagatran on ischemic events and death in patients with atrial fibrillation after acute myocardial infarction in the efficacy and safety of the oral direct thrombin inhibitor ximelagatran in patients with recent myocardial damage (ESTEEM) trial. Am Heart J 2008 Feb;155(2):382-7.
FFAACS	Lechat P, Lardoux H, Mallet A, Sanchez P, Derumeaux G, Lecompte T, et al. [Study of combined anticoagulant (fluindione)-aspirin therapy in patients with atrial fibrillation at high risk for thromboembolic complications. A randomized trial (FFAACS)]. [French]. Therapie 2000 Nov;55(6):681-9.
	Lechat P, Lardoux H, Mallet A, Sanchez P, Derumeaux G, Lecompte T, et al. Anticoagulant (fluindione)-aspirin combination in patients with high-risk atrial fibrillation. A randomized trial (Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontane; FFAACS). Cerebrovasc Dis 2001;12(3):245-52.
Hu 2006 (excl NMA)	Hu DY, Zhang HP, Sun YH, Jiang LQ. [The randomized study of efficiency and safety of antithrombotic therapy in nonvalvular atrial fibrillation: warfarin compared with aspirin]. Zhonghua Xin Xue Guan Bing Za Zhi 2006 Apr;34(4):295-8.
JAST	Sato H, Ishikawa K, Kitabatake A, Ogawa S, Maruyama Y, Yokota Y, et al. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial . Stroke 2006 Feb;37(2):447-51.

JNAFESP	Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation : a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation-Embolism Secondary Prevention Cooperative Study Group. Stroke 2000 Apr;31(4):817-21.
LASAF	Posada IS, Barriales V. Alternate-day dosing of aspirin in atrial fibrillation 1714. American Heart Journal 138(1 I)()(pp 137-143), 1999 Date of Publication: 1999 1999;(1 I):137-43.
Lu 2006 (excl NMA)	Lu Y, Zhang J. Anticoagulant treatment on chronic non-valvular atrial fibrillation in the elderly patients. [Chinese]. Chinese Journal of Emergency Medicine 15(1)()(pp 54-56), 2006 Date of Publication: Jan 2006 2006;(1):54-6.
MWNAF	Pengo V, Zasso A, Barbero F, Banzato A, Nante G, Parissenti L, et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. American Journal of Cardiology 1998 Aug 15;82(4):433-7.
NASPEAF	Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study . Journal of the American College of Cardiology 2004 Oct 19;44(8):1557-66.
PATAF	Hellemons BS, Langenberg M, Lodder J, Vermeer F, Schouten HJ, Lemmens T, et al. Primary prevention of arterial thromboembolism in non-rheumatic atrial fibrillation in primary care: randomised controlled trial comparing two intensities of coumarin with aspirin . BMJ 1999 Oct 9;319(7215):958-64.
Pengo 2010	Pengo V, Cucchini U, Denas G, Davidson BL, Marzot F, Jose SP, et al. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. Thromb Haemost 2010 Feb;103(2):442-9.
PETRO	Wallentin LC, Ezekowitz M, Simmers TA, Pedersen KE, Stangier J, Nehmiz G, et al. Safety and efficacy of a new oral direct thrombin inhibitor dabigatran in atrial fibrillation - a dose finding trial with comparison to warfarin. Eu Heart J 2005;26:482-3.
	Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, et al. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). American Journal of Cardiology 2007 Nov 1;100(9):1419-26.
RE-LY	Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361(12):1139-51.
	Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. N Engl J Med 2010;363:1875-6.
ROCKET – AF (not in SR)	Patel MR, Mahaffey KW, Garg J, Pan G et al; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91. Epub 2011 Aug 10.
SAFT	Edvardsson N, Juul-Moller S, Omblus R, Pehrsson K. Effects of low-dose warfarin and aspirin versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. Journal of Internal Medicine 2003 Jul;254(1):95-101.
SIFA	Amabile G, Matteoli S, Fattapposta F, Lavezzari M, Trappolini M, Heiman F, et al. [Italian Study on Atrial Fibrillation (SIFA): status report]. [Italian]. Cardiologia 1993 Dec;38(12:Suppl 1):327-32.
	Morocutti C, Amabile G, Fattapposta F, Nicolosi A, Matteoli S, Trappolini M, et al. Indobufen versus warfarin in the secondary prevention of major vascular events in nonrheumatic atrial fibrillation 1895. Stroke 28(5)()(pp 1015-1021), 1997 Date of Publication: May 1997 1997;(5):1015-21.
SPAF (excl NMA)	Design of a multicenter randomized trial for the Stroke Prevention in Atrial Fibrillation Study. The Stroke Prevention in Atrial Fibrillation Investigators. Stroke 1990 Apr;21(4):538-45.

(excl NMA)	Prevention of stroke in atrial fibrillation.[comment]. New England Journal of Medicine 1990 Aug 16;323(7):481-4.
(excl NMA)	McBride R, Anderson DC, Asinger RW, Newburg SM, Farmer CC, Wang K, et al. Preliminary report of the stroke prevention in atrial fibrillation study 2190. New England Journal of Medicine 322(12)()(pp 863-868), 1990 Date of Publication: 1990 1990;(12):863-8.
(excl NMA)	Stroke Prevention in Atrial Fibrillation Study. Final results . Circulation 1991 Aug;84(2):527-39.
SPAF II	Warfarin Compared to Aspirin for Prevention of Arterial Thromboembolism in Atrial Fibrillation. Cerebrovasc Dis 1992;2(6):332-41.
	Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study . Lancet 1994 Mar 19;343(8899):687-91.
	Chesebro JH, Wiebers DO, Holland AE, Bardsley WT, Litin SC, Meissner I, et al. Bleeding during antithrombotic therapy in patients with atrial fibrillation 1970. Archives of Internal Medicine 156(4)()(pp 409-416), 1996 Date of Publication: 26 Feb 1996 1996;(4):409-16.
SPAF III	Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial . Lancet 1996 Sep 7;348(9028):633-8.
	Stroke Prevention In Atrial Fibrillation Investigators. The stroke prevention in atrial fibrillation III study: Rationale, design, and patient features. Journal of Stroke & Cerebrovascular Diseases 1997 Jul;6(5):341-53.
SPINAF	Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators.[see comment][erratum appears in N Engl J Med 1993 Jan 14;328(2):148]. New England Journal of Medicine 1992 Nov 12;327(20):1406-12.
SPORTIF II (excl NMA)	Petersen P, Grind M, Adler J, SPORTIF II, I. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. Journal of the American College of Cardiology 2003 May 7;41(9):1445-51.
SPORTIF III	Olsson SB, Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial . Lancet 2003 Nov 22;362(9397):1691-8.
SPORTIF V	Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial . JAMA 2005 Feb 9;293(6):690-8.
SPORTIF III/V	Halperin JL, Executive Steering Committee. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). American Heart Journal 2003 Sep;146(3):431-8.
Vemmos 2006	Vemmos KN, Tsivgoulis G, Spengos K, Manios E, Xinos K, Vassilopoulou S, et al. Primary prevention of arterial thromboembolism in the oldest old with atrial fibrillation - A randomized pilot trial comparing adjusted-dose and fixed low-dose coumadin with aspirin 722. European Journal of Internal Medicine 17(1)()(pp 48-52), 2006 Date of Publication: Jan 2006 2006;(1):48-52.
WAPSO	Rash A, Downes T, Portner R, Yeo WW, Morgan N, Channer KS. A randomised controlled trial of warfarin versus aspirin for stroke prevention in octogenarians with atrial fibrillation (WASPO). Age & Ageing 2007 Mar;36(2):151-6.

The following typographical errors are in the NMA report

SPIF – should read SPINAF
MWF – should read MWNAF
SPEAF – should read NASPEAF
JFESP - should read JNAFESP.

A8. **Priority request**: For each outcome assessed in the network meta-analysis please provide:

a. the quantification of heterogeneity (i.e. the value for tau).

b. the number of unconstrained data points and the residual deviance.

Please consider the table below:

	Tau	Residual deviance	Unconstrained data points
Composite Outcome	[redacted]	[redacted]	[redacted]
CV Mortality	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]
GI Bleed	[redacted]	[redacted]	[redacted]
Haemorrhagic Stroke	[redacted]	[redacted]	[redacted]
Ischemic Stroke	[redacted]	[redacted]	[redacted]
Major haemorrhage	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
Minor Bleed	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]
Systemic Embolism	[redacted]	[redacted]	[redacted]
Transient ischemic attack	[redacted]	[redacted]	[redacted]
Total Stroke	[redacted]	[redacted]	[redacted]

A9. Please provide the number of UK centres that were there in ROCKET-AF and the number of patients from the UK that were randomised.

There were 29 sites in the UK, with 6 sites not recruiting any patients. The total number of patients in the UK was 206.

A10. In the network meta-analysis, please clarify why the ROCKET-AF safety on treatment data set was chosen rather than the ITT data set, which was used for all other trials included in the network meta-analysis (page 18 Oxford Outcomes network meta-analysis report).

The pre-specified analysis was used from each trial. The primary goal of ROCKET-AF was to establish non-inferiority of rivaroxaban versus warfarin in the per protocol on treatment population. In ROCKET AF, if non-inferiority was declared in the per protocol population, then superiority on the primary efficacy endpoint was then to be based on on-treatment data from the safety population. In order to test robustness of the pre-specified "on-treatment" analysis, sensitivity testing for non-inferiority and superiority was also performed in the intention-to-treat (ITT) population – this analysis was not part of the hierarchical closed testing procedure. As such it was decided that the most appropriate comparison to make in the NMA was on the pre-specified safety on treatment population.

Further, the ITT population in ROCKET AF is not comparable with ITT in the other trials in the NMA due to the prolonged "off treatment" period - in the full ITT (to site notification), there was a median of 117 days of follow-up assigned medication i.e. patients were off randomised treatment.

A11. Please confirm whether in ROCKET-AF the coatings of the "matching oral warfarin placebo" and matching oral rivaroxaban placebo" were the same as those used in the corresponding "active" tablets.

Rivaroxaban was provided as round red tablets. The tablets were film-coated with hypromellose, macrogol, and titanium dioxide/ferric oxide red. The matching placebo tablets had a film-coat of hypromellose, macrogol, and titanium dioxide/ferric oxide red. There were no noticeable visible differences between the 2 rivaroxaban strengths and the matching placebo tablets.

The warfarin tablets were round and single-scored, dye free, and debossed on one side with 'WAR' and the numeric strength of the tablet (1 mg, 2.5 mg, and 5 mg). Placebo tablets matched the appearance of the active tablets. Matching placebo tablets were supplied in the same shape, color, and with the same strength markings as the active tablets.

A12. Please clarify whether patients randomly assigned to warfarin with moderate renal impairment (i.e. a baseline creatinine clearance 30-49ml/min) were treated any differently to those with baseline creatinine clearance >49ml/min (outlined on page 41 of the manufacturer's submission).

Warfarin patients received the same therapy regardless of renal function.

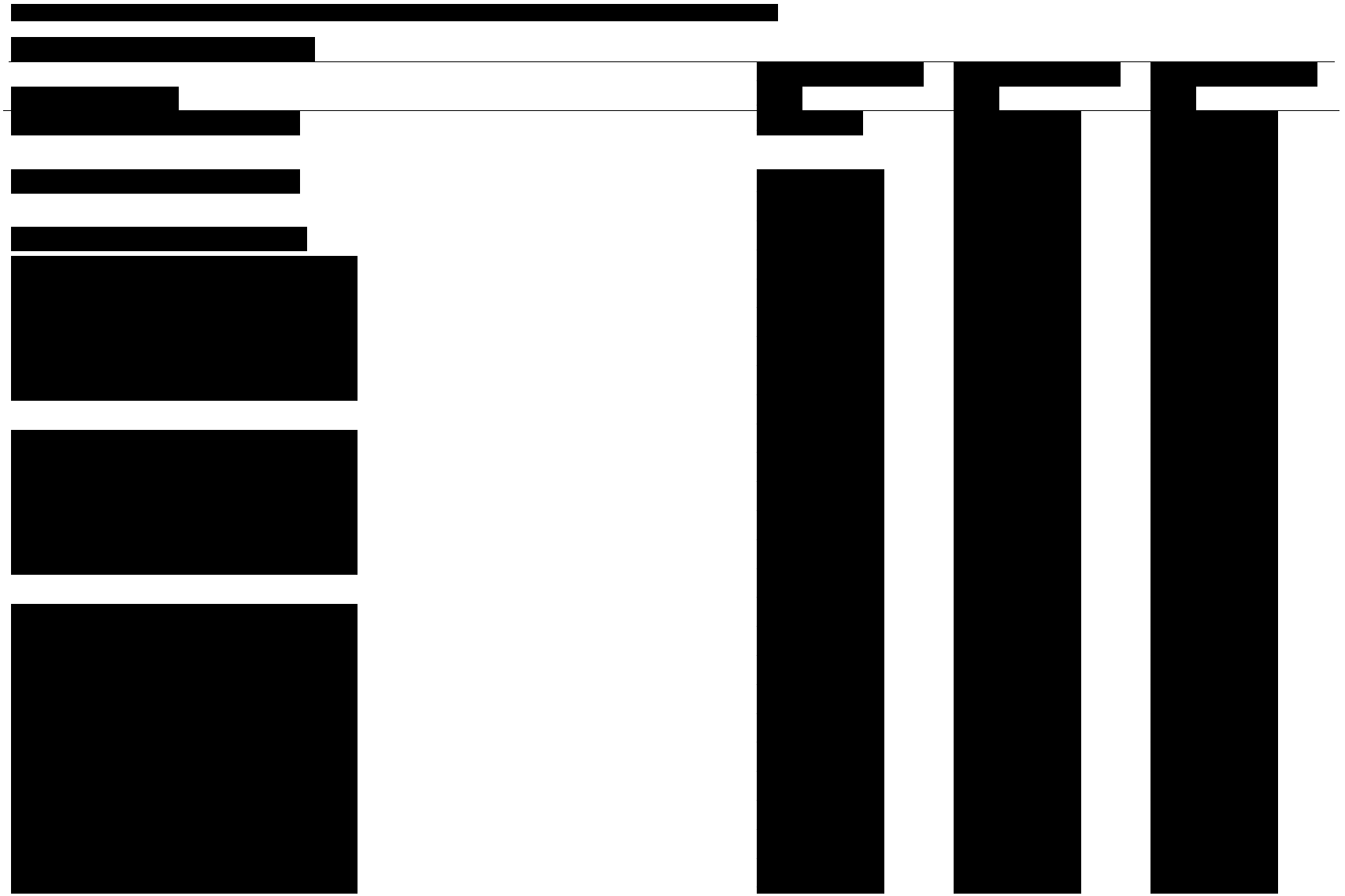
A13. The ERG note that there is a large difference between the ITT (to site notification) analysis results and the safety on treatment analysis results for primary endpoint of ROCKET-AF in the North America subgroup (Hazard ratio 0.95 vs. 0.58, as summarised in the table below; taken from Figures 11 and 12 in the submission). Please can you explain the potential reasons for this apparent discrepancy?

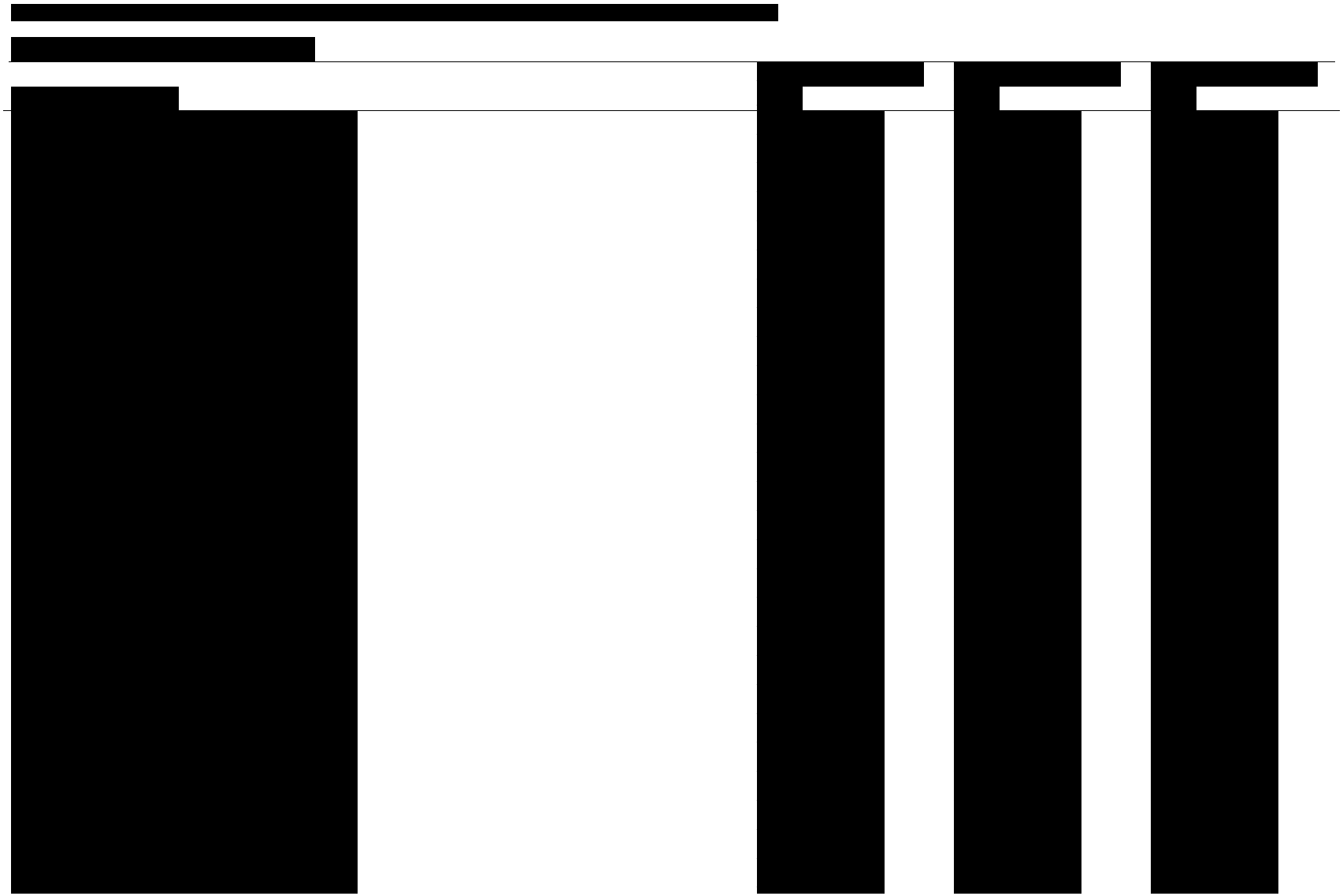
Population	**Event rate**		**Hazard ratio Rivaroxaban vs Warfarin**
	Rivaroxaban	**Warfarin**	
ITT to site notification	47/1339 (3.51%)	50/1342 (3.73%)	0.95 0.64 to 1.42
Safety population/on treatment	20/1334 (1.5%)	36/1339 (2.69%)	0.58 0.34 to 1.01

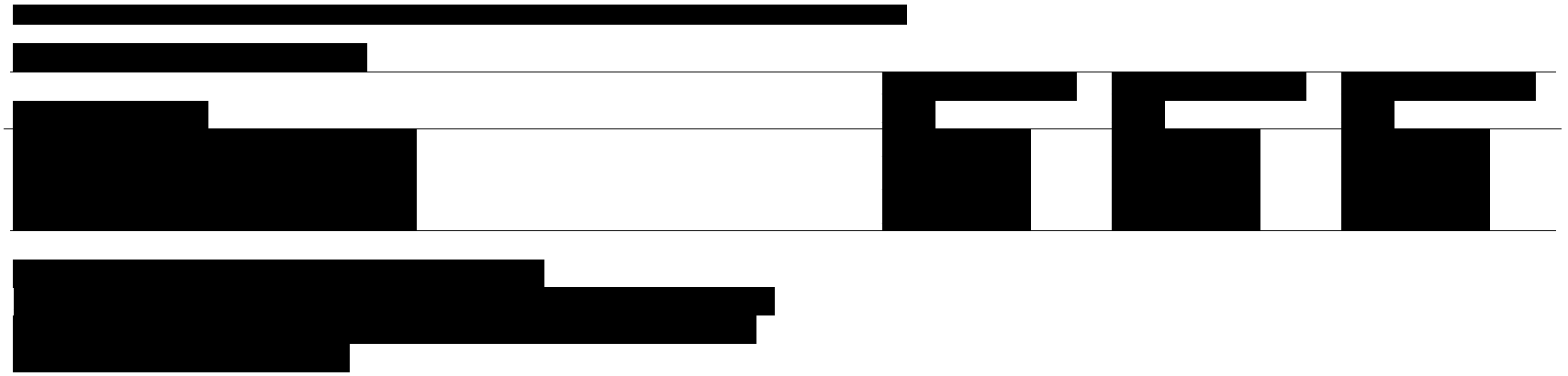
We cannot give a rationale for this and suggest that this apparent discrepancy is likely to be a chance finding. In any data set, such findings are likely to occur when extensive sub-group analysis is run with small patient numbers.

A14. Please provide the numbers of people in each of the ROCKET AF trial arms who had a temporary disruption to treatment and the mean length (and range) and reasons for the interruptions.

Please see the table on the next page.



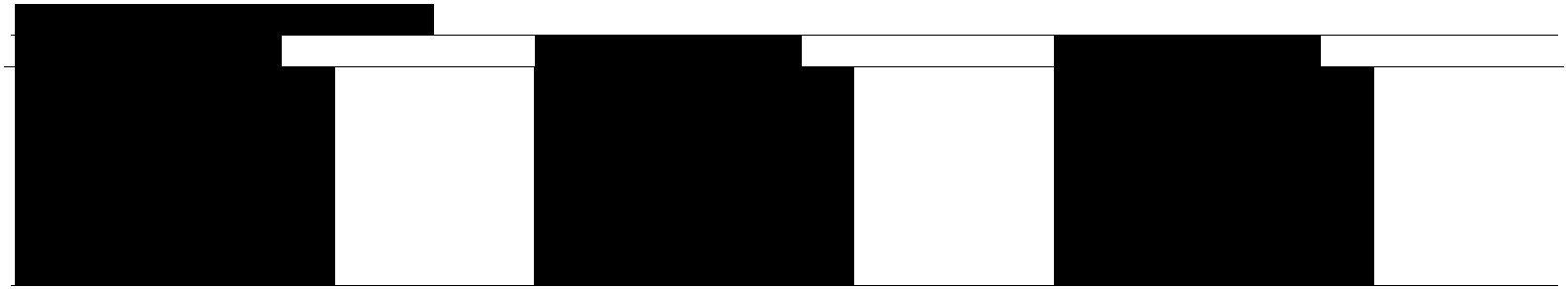




A15. Please provide the numbers of people who received the 15mg dose of rivaroxaban in the ITT and per protocol populations

Please see the table on the following page.

[redacted]



[redacted]

A16. In the submission it states that over 50% of people in ROCKET-AF received treatment for >18 months, but no further details are provided. Please complete the table below to provide details on the number of people who discontinued their randomised study drug at each of the time periods listed below. Please also provide the overall mean, median and range of treatment duration for the ITT, per protocol and safety on treatment populations.

Patients can only discontinue if they have previously taken a dose of study drug. The safety population is defined as all ITT patients who had taken at least one dose of study medication. Patients in the ITT population may not have received study medication, therefore the measure of duration of treatment only makes sense in the safety population. Thus, we have provided the information in the safety population.

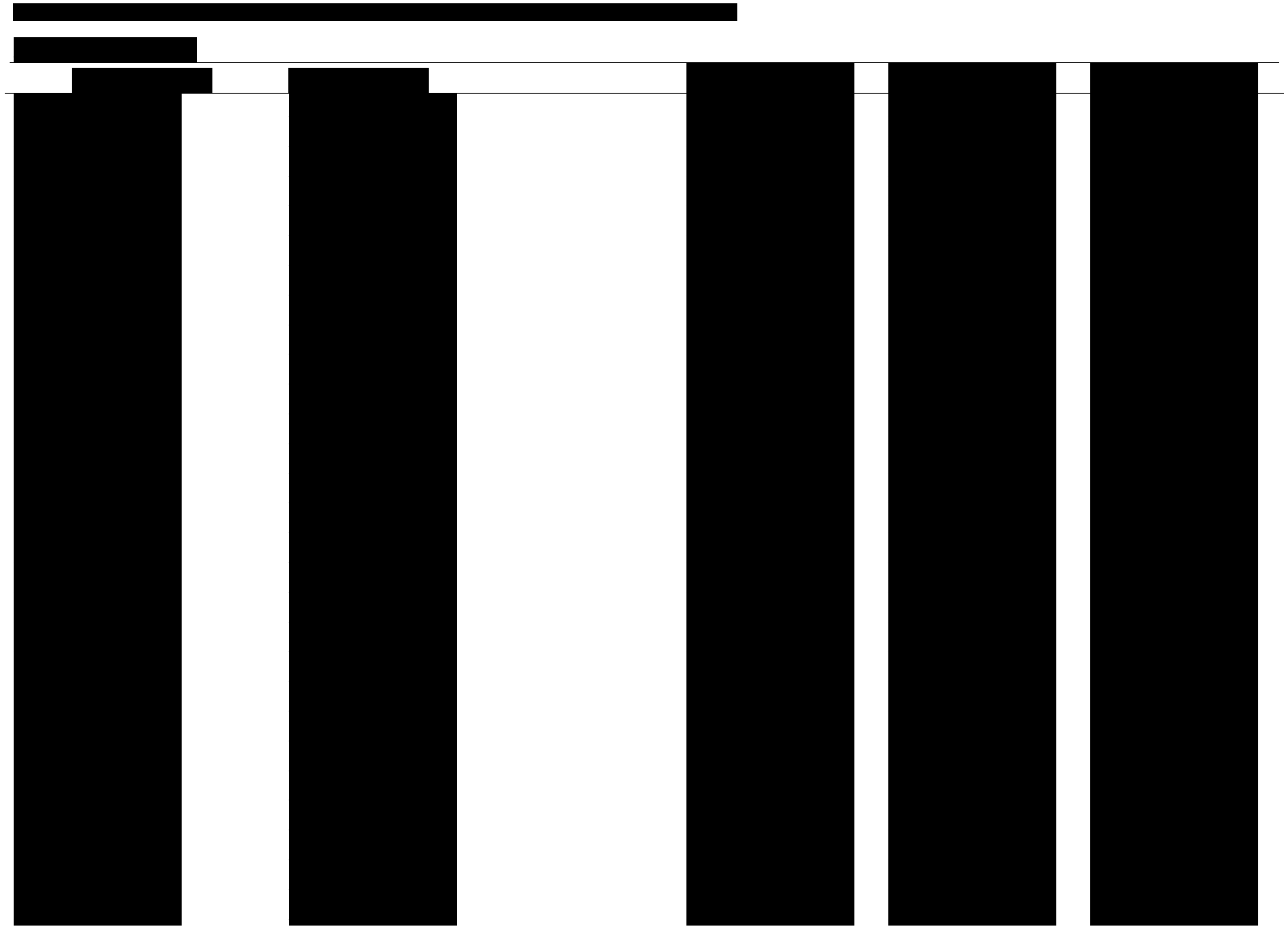
Cumulative Total Treatment Duration of Active Study Medications
(Safety Analysis Set)

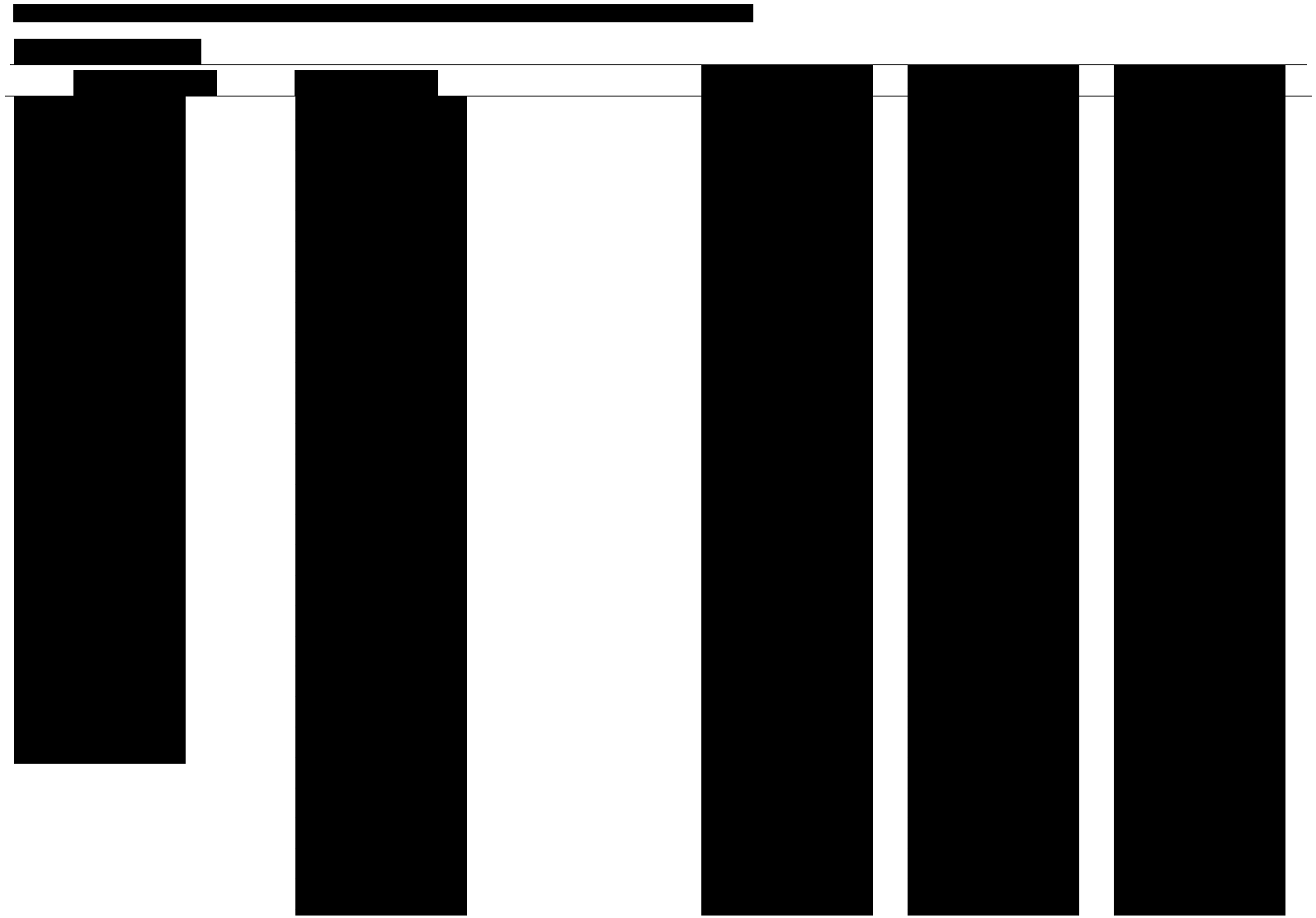
Cumulative Treatment Duration	Rivaroxaban (N=7111) n(%)	Warfarin (N=7125) n(%)	Total (N=14236) n(%)
≥ One Dose	7111 (100)	7125 (100)	14236 (100)
≥ 1 Month	6800 (95.63)	6854 (96.20)	13654 (95.91)
≥ 3 Months	6477 (91.08)	6551 (91.94)	13028 (91.51)
≥ 6 Months	6089 (85.63)	6222 (87.33)	12311 (86.48)
≥ 9 Months	5800 (81.56)	5888 (82.64)	11688 (82.10)
≥ 12 Months	5558 (78.16)	5624 (78.93)	11182 (78.55)
≥ 18 Months	4001 (56.26)	4074 (57.18)	8075 (56.72)
≥ 24 Months	2512 (35.33)	2571 (36.08)	5083 (35.71)
≥ 30 Months	1057 (14.86)	1062 (14.91)	2119 (14.88)
≥ 36 Months	141 (1.98)	147 (2.06)	288 (2.02)
≥ 42 Months	1 (0.01)	1 (0.01)	2 (0.01)
Mean (days)	572.23	579.86	576.05
SD	294.66	290.08	292.39
Min (days)	1	1	1
Q1 (days)	396	404	399
Median (days)	589	593	590
Q3 (days)	805	810	807
Max (days)	1263	1263	1263

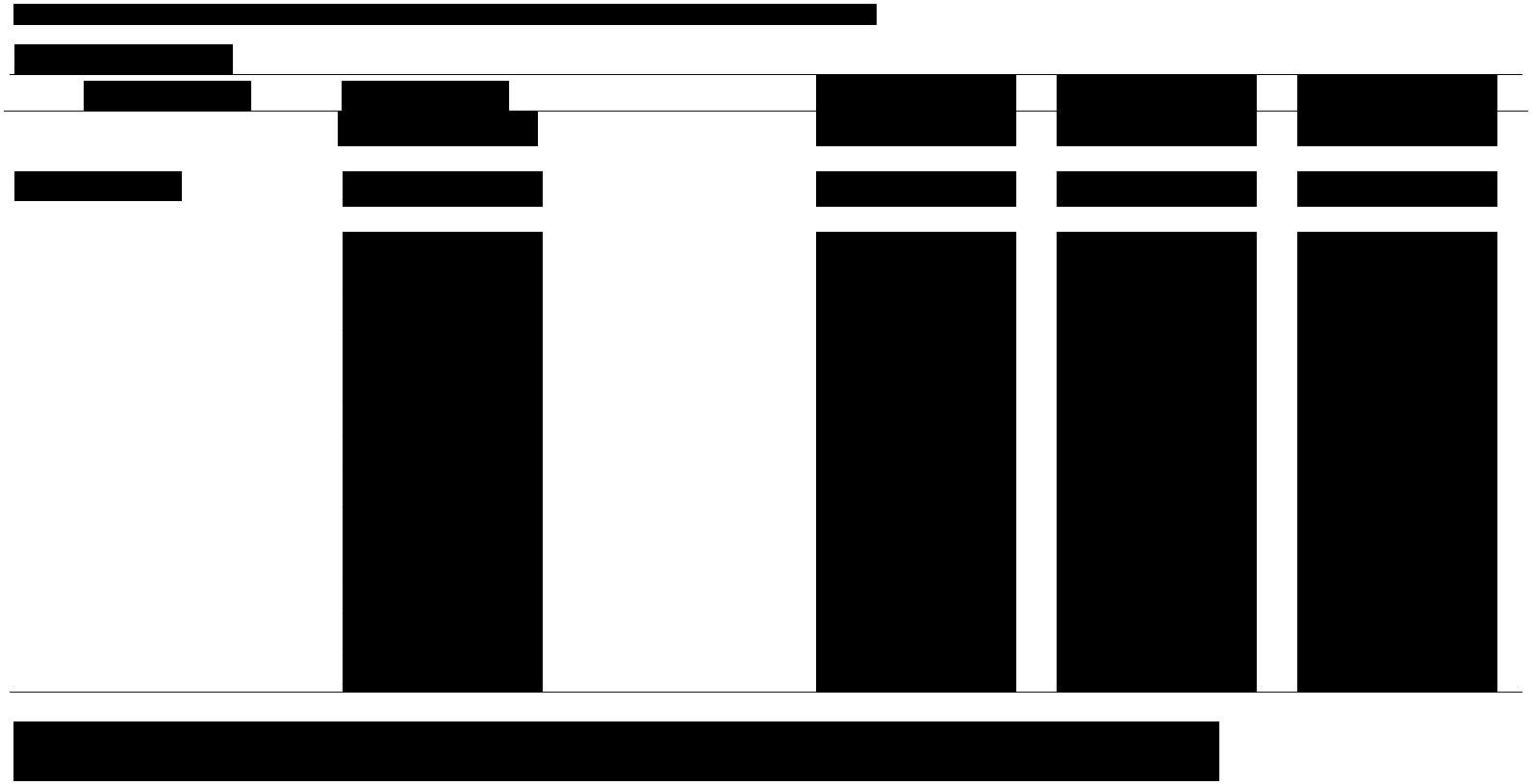
Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Total treatment duration = last dose date - first dose date + 1.
Note: 1 month = 30 days.
tsub008pb_rex01.rtf generated by rex01.sas, 02NOV2010 15:50

A17. Please provide details of the ITT treatment discontinuation rates in ROCKET-AF for each of the region subgroups in each of the trial arms, along with an itemised breakdown of the reasons for treatment discontinuation.

Patients can only discontinue if they have previously taken a dose of study drug. The safety population is defined as all ITT patients who had taken at least one dose of study medication. Patients in the ITT population may not have received study medication, therefore the measure of discontinuation rates only makes sense in the safety population. Thus, we have provided the information in the safety population.

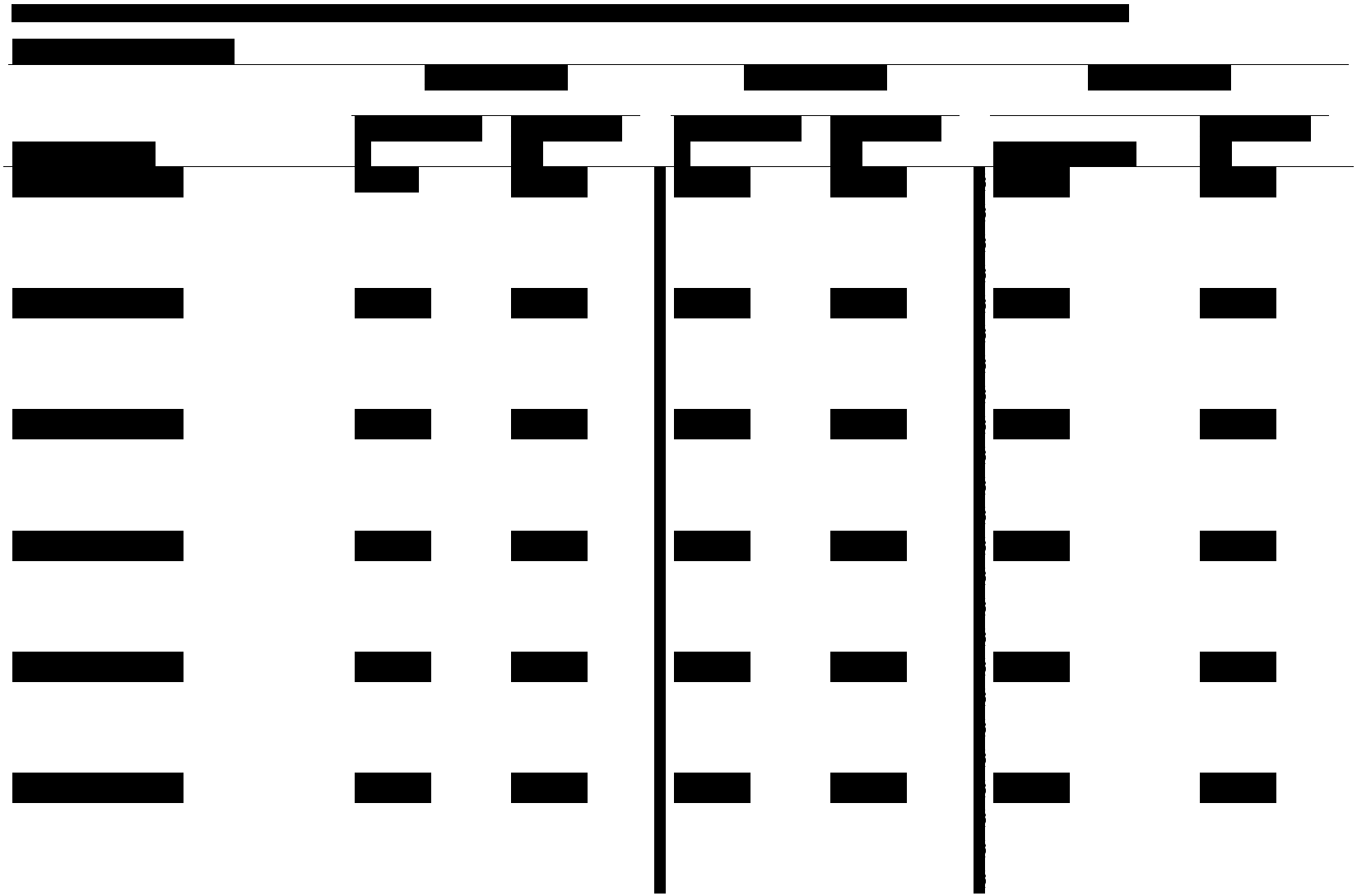


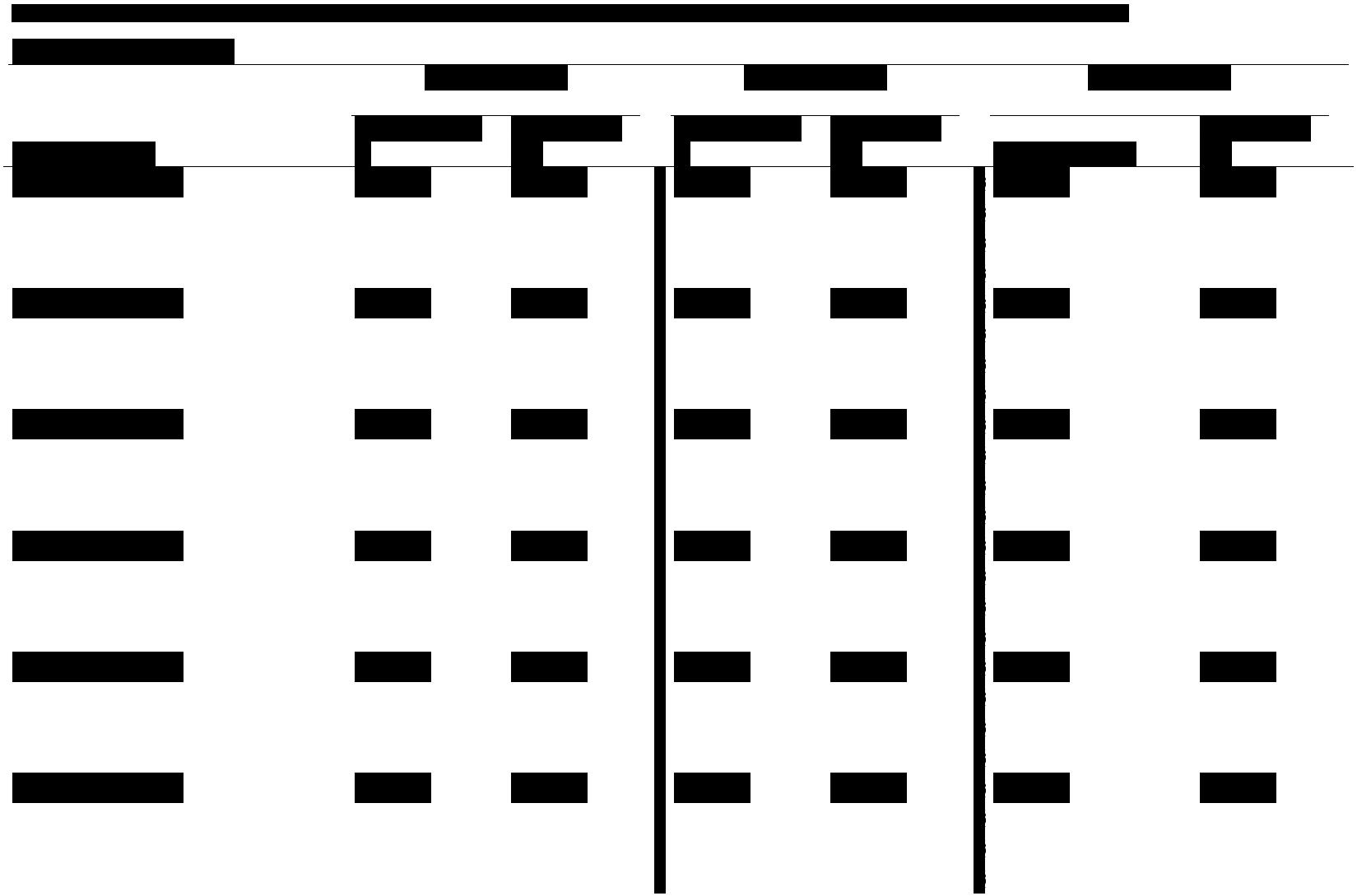


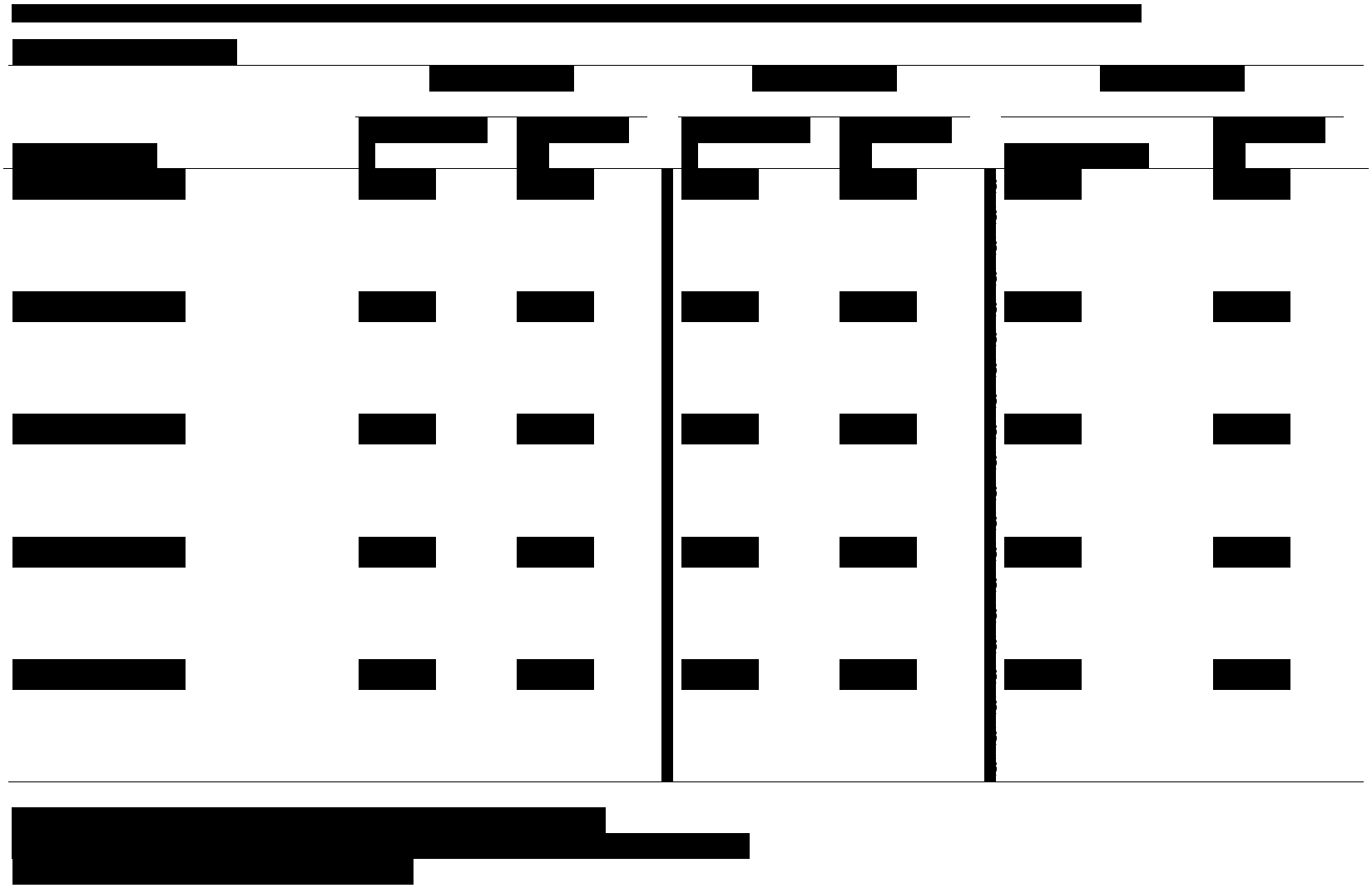


A18. Please complete the table below to provide a breakdown by the types and frequency of adverse event that led to treatment discontinuation in each of the ROCKET-AF trial arms for the ITT population. Please complete similar tables for the per protocol and safety on treatment populations.

Patients can only have an adverse event and discontinue if they have previously taken a dose of study drug. The safety population is defined as all ITT patients who had taken at least one dose of study medication. Patients in the ITT population may not have received study medication, therefore the measure of adverse events leading to treatment discontinuation only makes sense in the safety population. Thus, we have provided the information in the safety population.







A19. Please expand on the reasons for protocol violations that led to exclusion of the data from one site (the GCP violating site) from all the analyses in ROCKET AF.

All of the efficacy analyses excluded data from one site in the Czech Republic, from which data was deemed unreliable due to violations in good clinical practice guidelines (GCP). Data from this site was deemed to be unreliable due to evidence that source documents had been modified so subjects appeared to meet Inclusion/Exclusion criteria for enrollment into the study.

A20. Please expand on the decision to use the total ROCKET AF population in the submission rather than the data from the Western Europe and North America subgroups, given that the TTR for the whole trial population is lower than that typically reported for the UK and seen in other clinical trials, for example, e.g. RE-LY.

The decision was taken to use the total ROCKET AF population as it would not be appropriate to present data from just two geographical regions. Furthermore, such analyses were not pre-specified. This would inevitably affect the interpretation of the results as the study was not powered for such analysis.

TTR is lower than that reported in other studies however, various methods have been used in clinical trials to calculate the TTR, and the results of all of these methods depend on details such as what therapeutic range is used, whether warfarin naïve patients are included or only patients already on established therapy, whether INRs obtained during invasive procedures when warfarin therapy might be interrupted are included, and whether different oral anticoagulant preparations are included. This makes cross study comparisons challenging.

Patient clinical history may have impacted on the TTR achieved. ROCKET AF is a unique study because it included patients with many risk factors for stroke and comorbid conditions. The TTR values observed in ROCKET AF are consistent with those expected in such a group of patients. Heart failure, diabetes, and prior stroke, all components of the CHADS2 classification system, have been shown in other studies to be moderate predictors of lower TTR *[Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Patient characteristics associated with oral anticoagulation control: results of the Veterans AffaiRs Study to Improve Anticoagulation (VARIA). J Thromb Haemost 2010 Oct;8(10):2182-91]*

Importantly, in ROCKET AF, the centre time in therapeutic range (TTR) achieved for warfarin did not affect the outcomes seen with rivaroxaban i.e. the rivaroxaban treatment effect is independent of the level of INR control in the warfarin group. The overall benefit-risk assessment favours rivaroxaban even amongst centers with the best warfarin management *[Supplement to: Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011. DOI: 10.1056/NEJMoa1009638.]*

A21. Please complete the table below to provide details of bleeding adverse events in each trial arm in ROCKET AF by age using the following subgroups for the ITT population:

a. <65;

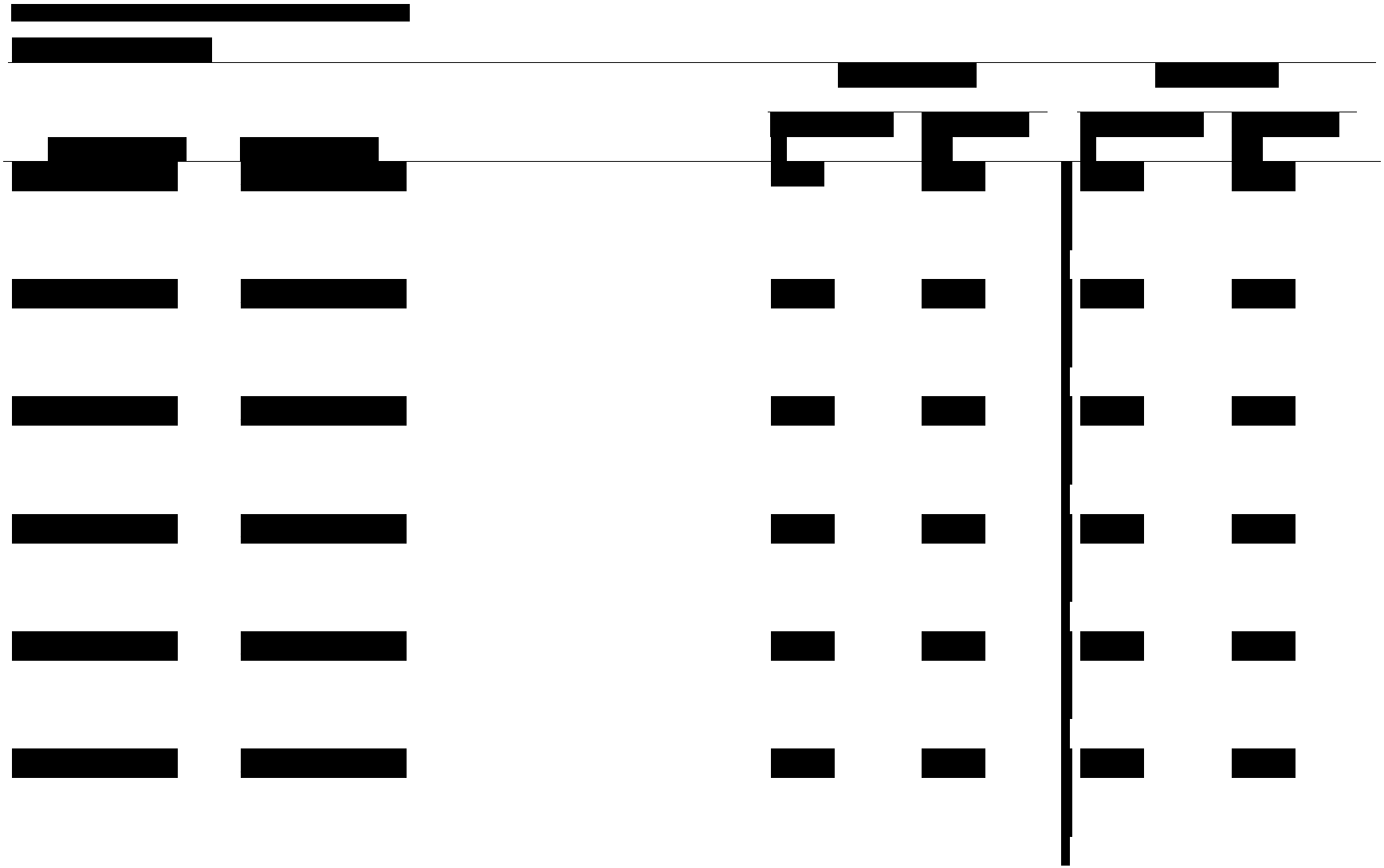
b. ≥65 and <75;

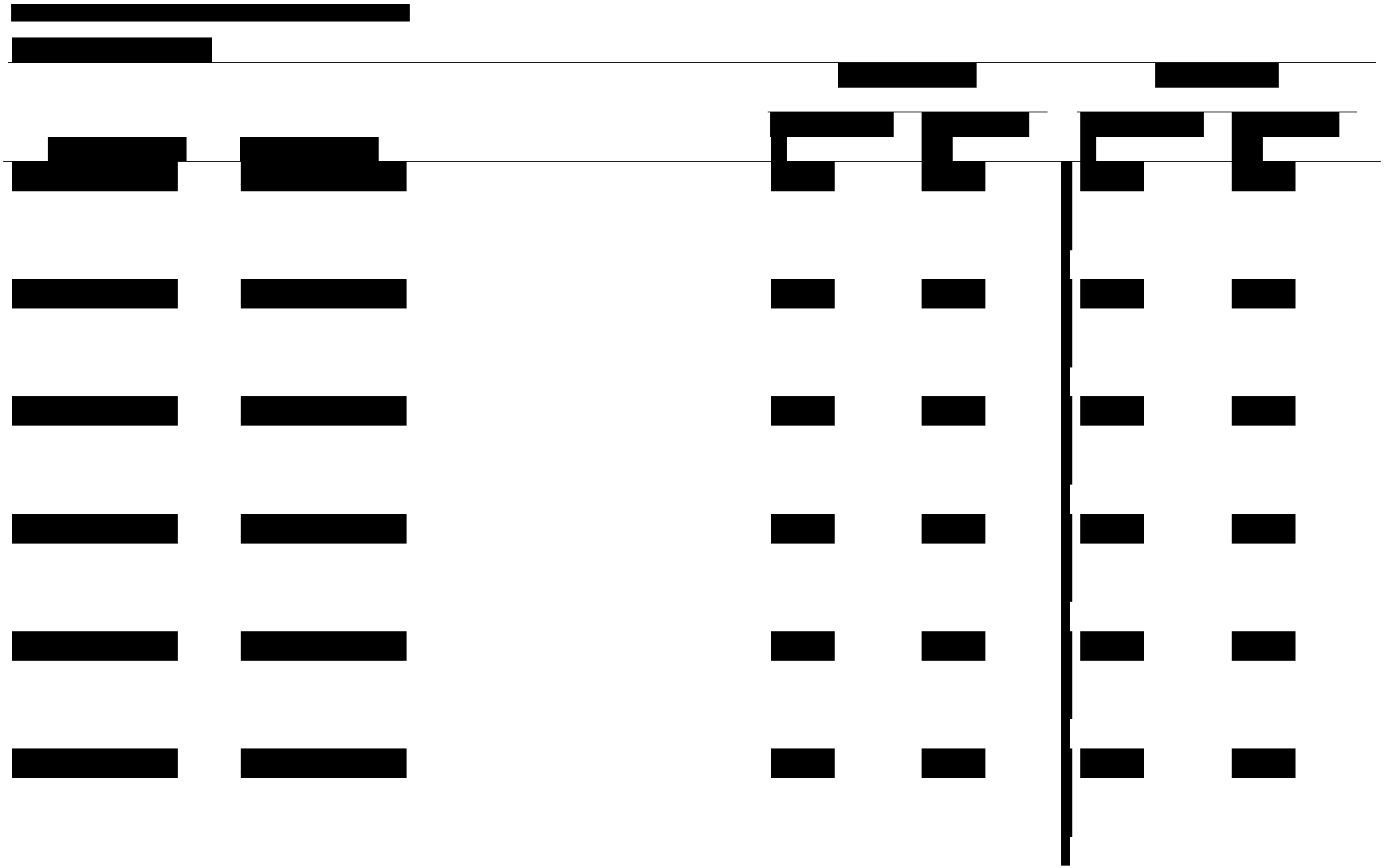
c. ≥75 and <85;

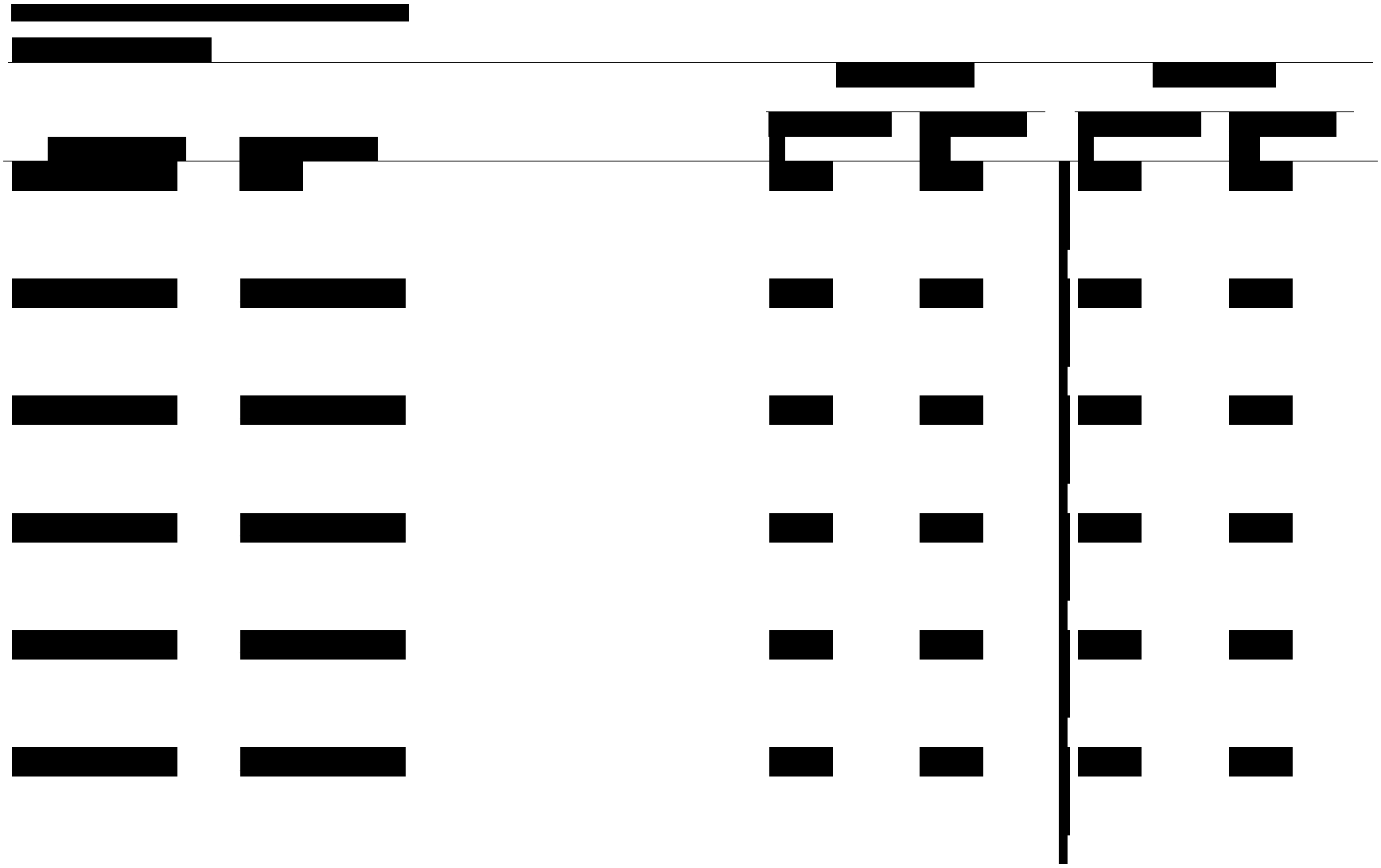
d. ≥85.

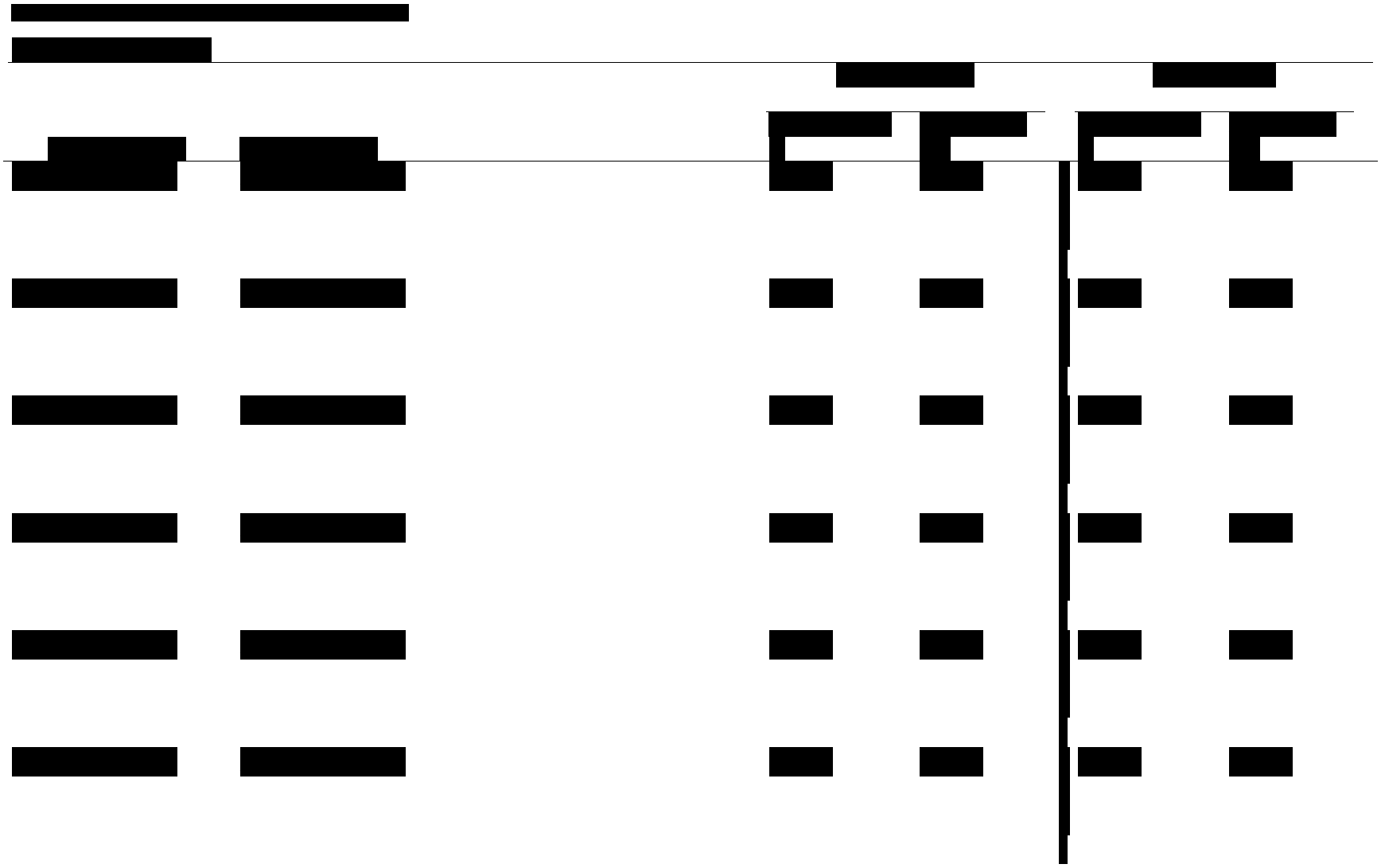
Please complete similar tables for the per protocol on treatment and safety on treatment populations.

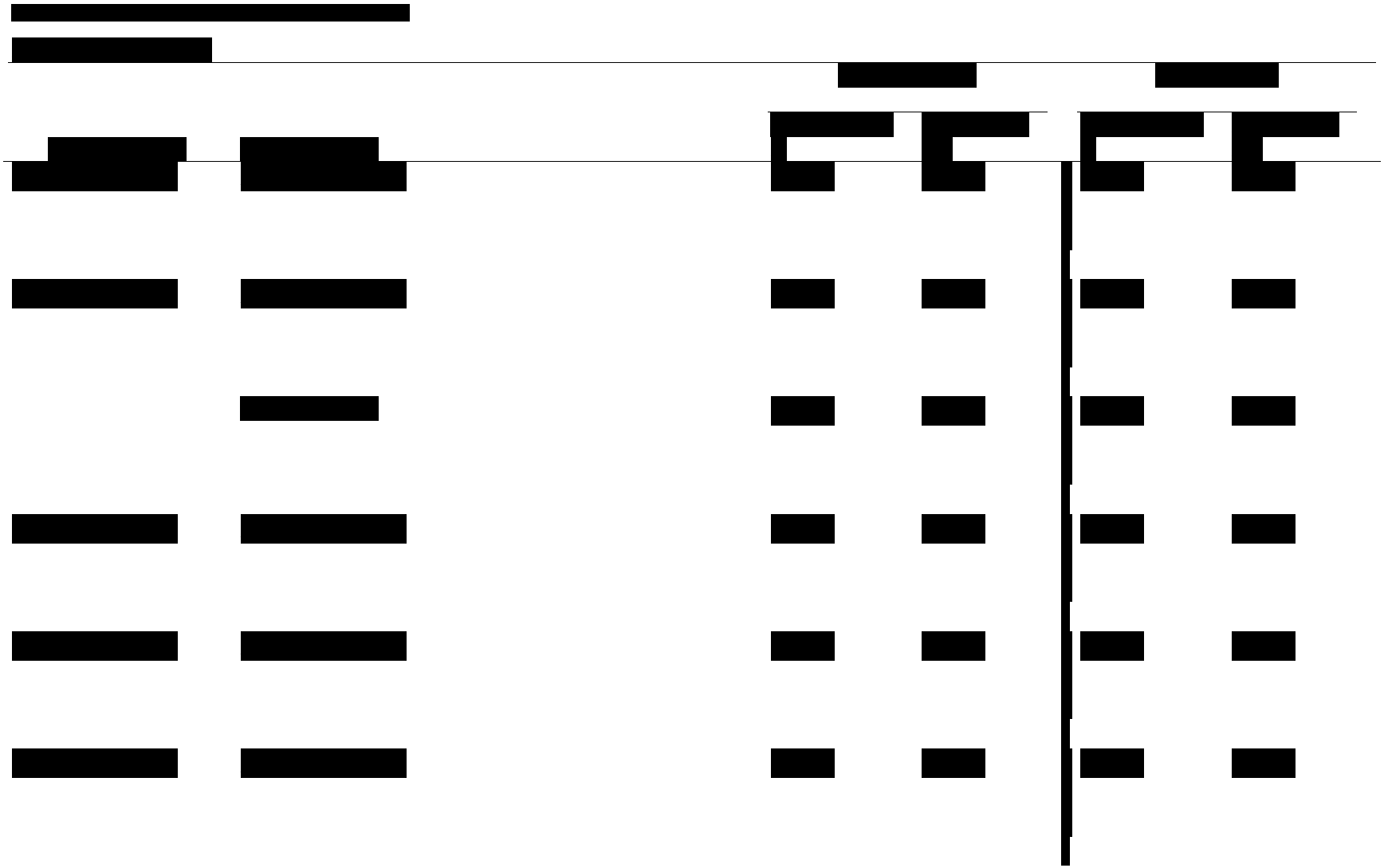
The safety on-treatment summaries are the pre-planned and most relevant summaries for evaluation of safety events. The evaluations are provided as requested with the exception that “minor” bleed was not a CEC adjudicated category of events and is omitted. In addition ‘gastrointestinal events” are interpreted to mean Major bleeds with a site equal to gastrointestinal lower- or gastrointestinal upper- extremity.

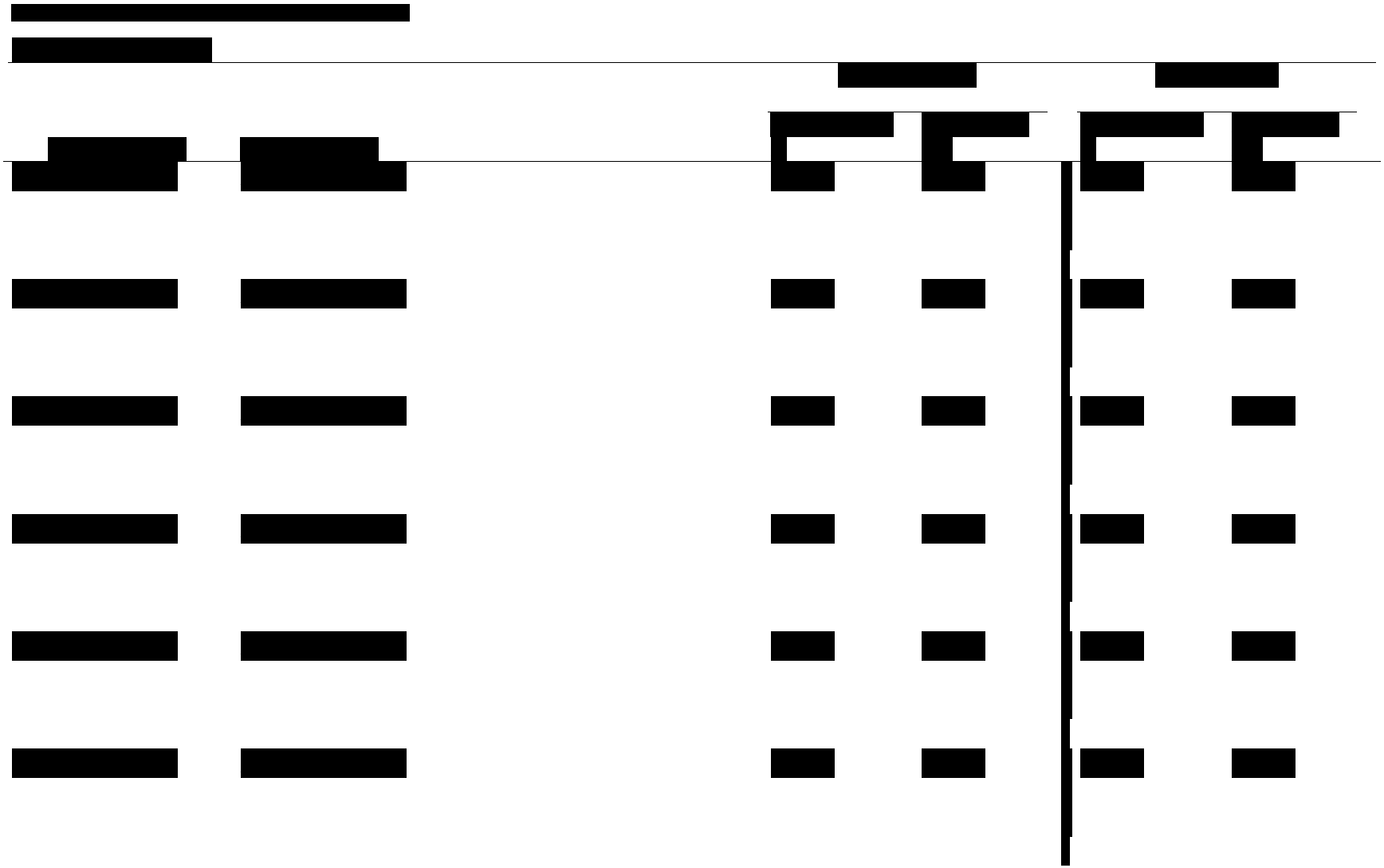


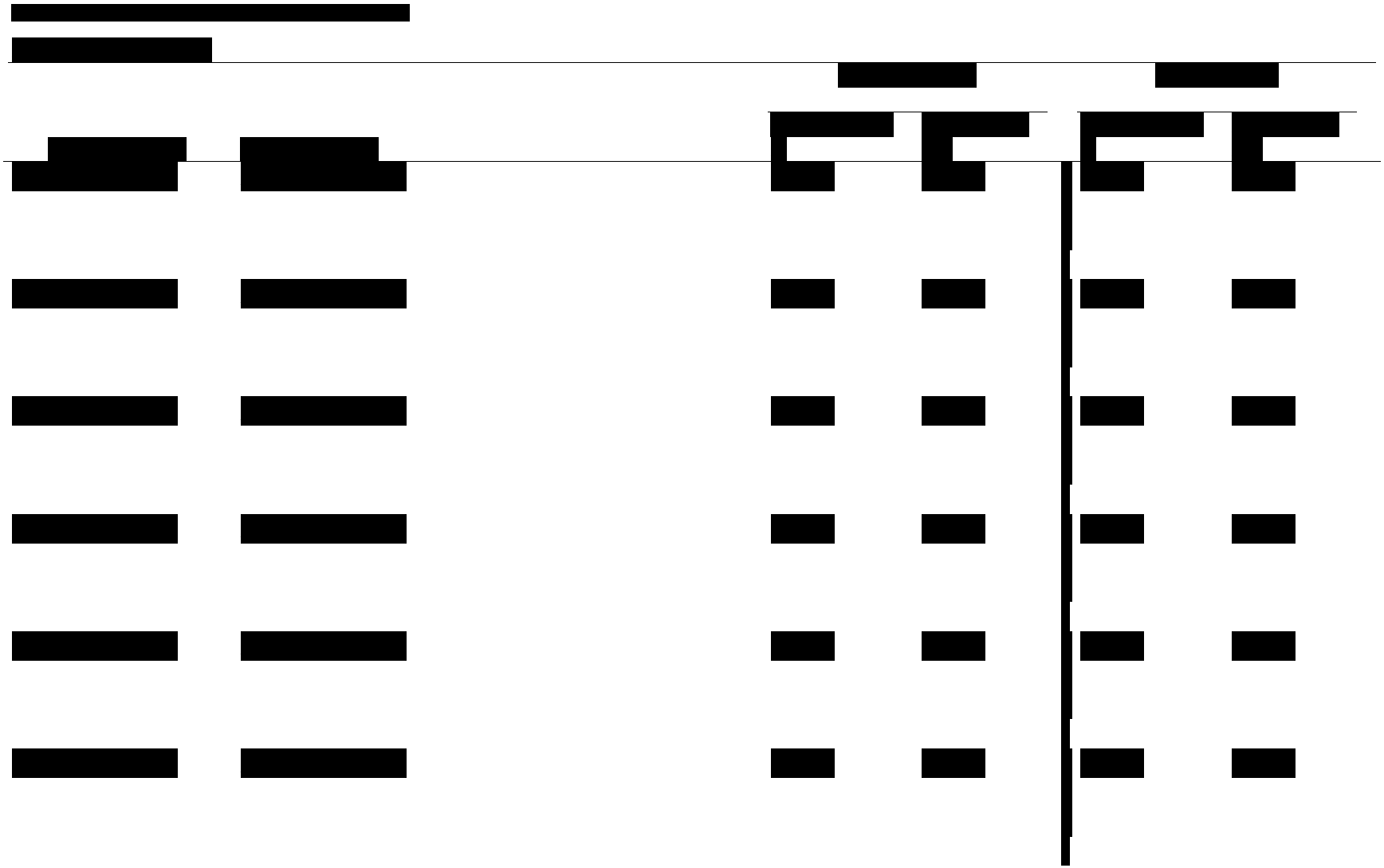


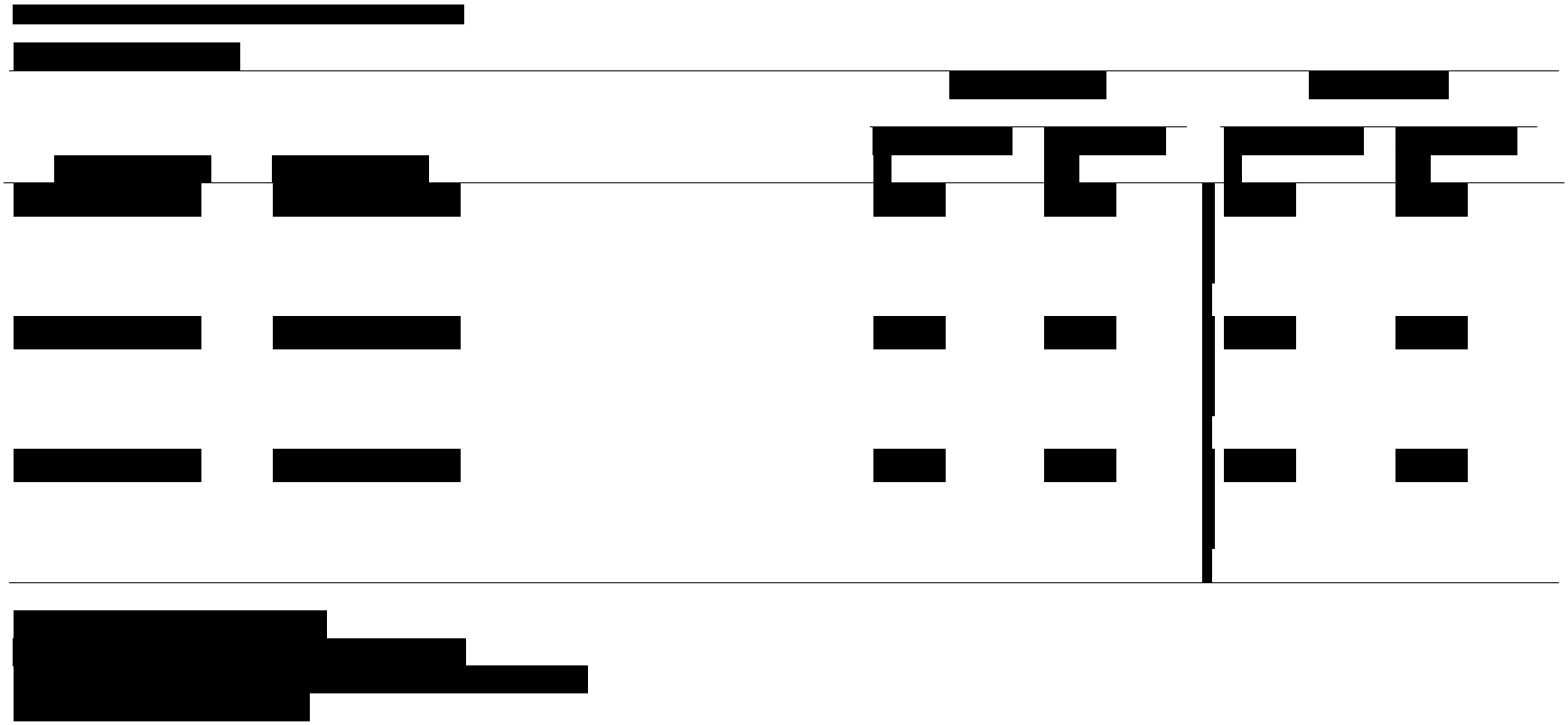












A22. Please provide the definition used in ROCKET AF for no prior VKA use (i.e. were they warfarin naïve patients?).

Prior VKA use was defined as VKA use for 6 weeks or longer at the time of screening. VKA naive was defined as no use of VKA within 6 weeks prior to randomisation.

This means that a patient who stopped taking warfarin 2 months prior to randomisation was considered naive.

VKA naïve was therefore made up of:

- patients with no prior VKA use
- patients who may have used VKA's previously but with no use within 6 weeks prior to randomisation.

A23. Please provide details of any protocol amendments made in ROCKET AF and give the reasons for any amendments.

The original protocol was issued on 04 October 2006 [redacted]

Amendment INT-1 (08 June 2007)

The major changes implemented in Amendment INT-1 included:

- The screening period was extended and changed to 30 days (Day –30 to Day 1) from 14 days;
- Clarified the time window and modified thresholds for unblinded INR testing before randomization;
- Modified acceptable documentation of atrial fibrillation. [redacted] This modification did not alter the patient population, i.e., non valvular atrial fibrillation;
- Modified the definition of the stratification factor for prior VKA use which was defined as VKA use for 2 weeks or longer at the time of screening and changed to VKA use for 6 weeks or longer at the time of screening;
- Clarification that annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty were not exclusion criteria;
- Decreased the waiting time before enrollment for subjects with disabling strokes as well as non-disabling strokes, which aligned with accepted standards of care;
- Clarified that systemic treatment with strong inhibitors of cytochrome P450 3A4 was excluded;
- Clarified that strong inducers of cytochrome P450 3A4 such as rifampin were excluded based on the results of a drug interaction study;
- Clarified INR frequency during elective invasive procedures;
- Clarified and modified when unblinded INRs should be performed when switching from blinded study drug to open-label VKA;
- [redacted]

- Clarified that a Human immunodeficiency virus (HIV) assay was to be done if clinically indicated and only after consent from the subject was obtained;
- Added computed tomography (CT) scanning and magnetic resonance imaging (MRI) to ensure appropriate documentation of strokes;

[redacted]

Amendment INT-2 (13 February 2009)

Due to the low rate of enrollment into the originally planned PK/PD component of the study, the protocol was amended (INT-2) to facilitate completion of this protocol component.

[redacted]

The major changes implemented in Amendment INT-2 included:

- Terminology associated with the original rich PK and PD sampling approach was replaced with terminology appropriate to the matched PK and PD approach of the new substudy;

[redacted]

- Added the intention to include subjects with moderate renal impairment in the PK and PD substudy.

[redacted]

A24. Please explain the nature of the protocol violations leading to exclusion of people from the per protocol analysis in ROCKET-AF.

[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]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

A25. The NICE final scope lists transient ischaemic attacks and health-related quality of life as important outcome measures to be considered in the STA. Please can you clarify your reasons for not including data on these outcomes within the submission and where possible provide any available data.

TIA

When we agreed the scope with NICE, we believed that TIA would be an important outcome. In ROCKET AF, TIA was recorded as an adverse event, however it only occurred in [redacted] subjects [redacted] in the rivaroxaban arm and [redacted] subjects [redacted] in the warfarin arm. In line with standard practice, our submission reported the incidence of the 15 most frequent treatment-emergent adverse events and due to the low incidence TIA was not listed.

Health-related quality of life

Because of the double blind double dummy design of ROCKET-AF, differences between the two treatment arms would not be expected other than due to differences in number of events experienced. It was felt that the QOL impact of events could be captured using values for patients who had event, such as stroke from the literature rather than trying to collect this for the patients having an event in the trial.

Therefore, a systematic literature review was performed to identify health state utility values in atrial fibrillation, stroke, post-stroke, embolism, myocardial infarction and bleeding events occurring in a non-valvular atrial fibrillation population. The studies found were assessed according to pre-defined inclusion and exclusion criteria and data extracted as appropriate. The most appropriate values were applied in the economic modelling.

A26. Please complete the following table to provide data for all outcomes reported in ROCKET AF for each of the patient subgroups in the ITT, per protocol and safety on treatment populations:

a. Patients with and without prior use of vitamin K antagonists at baseline.

b. North America region.

c. Western Europe region.

d. INR control as measured by percentage time in therapeutic range (TTR) for people in the warfarin group with TTR <60% and ≥60% compared with the rivaroxaban total population.

It should be noted that the study was not powered to detect differences in these sub-groups, so they are provided for information only. Event numbers are low when sub-groups are examined which leads to greater uncertainty and it is therefore difficult to draw conclusions from such analyses.

As mentioned previously, safety outcomes are evaluated only on the safety population.

The following parameters are summarised for the ITT to site notification and per-protocol and safety on treatment populations/observation period:

- Composite
- Ischaemic stroke
- Haemorrhagic stroke / ICH
- Non-CNS systemic embolism
- Myocardial infarction
- Vascular death

- Mortality (all cause)

The following parameters are provided for the safety on-treatment population/observation period:

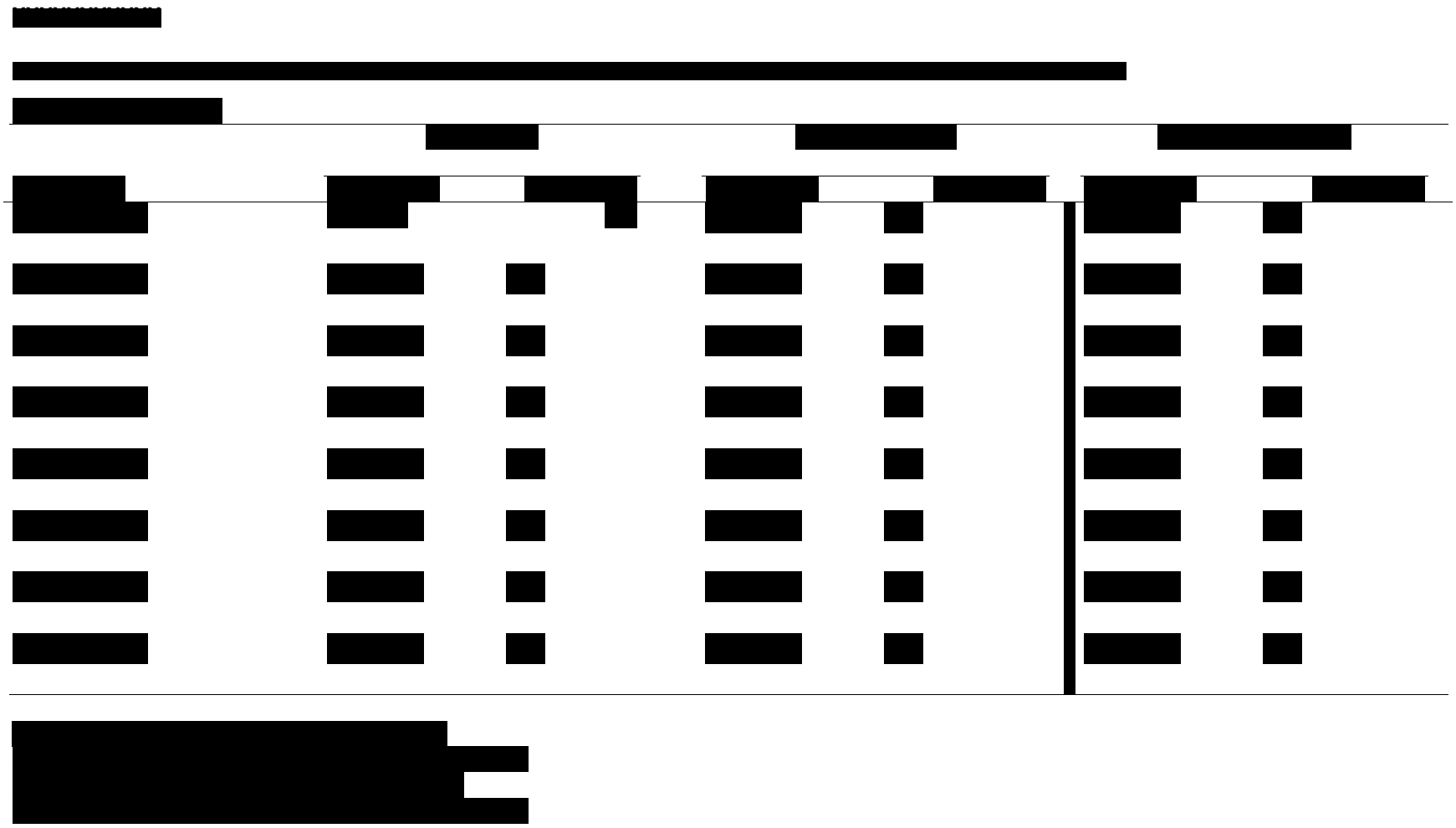
- Composite of all major and non-major clinically relevant bleeding events
- Major bleed
- Non-major clinically relevant bleeding
- Gastrointestinal bleed

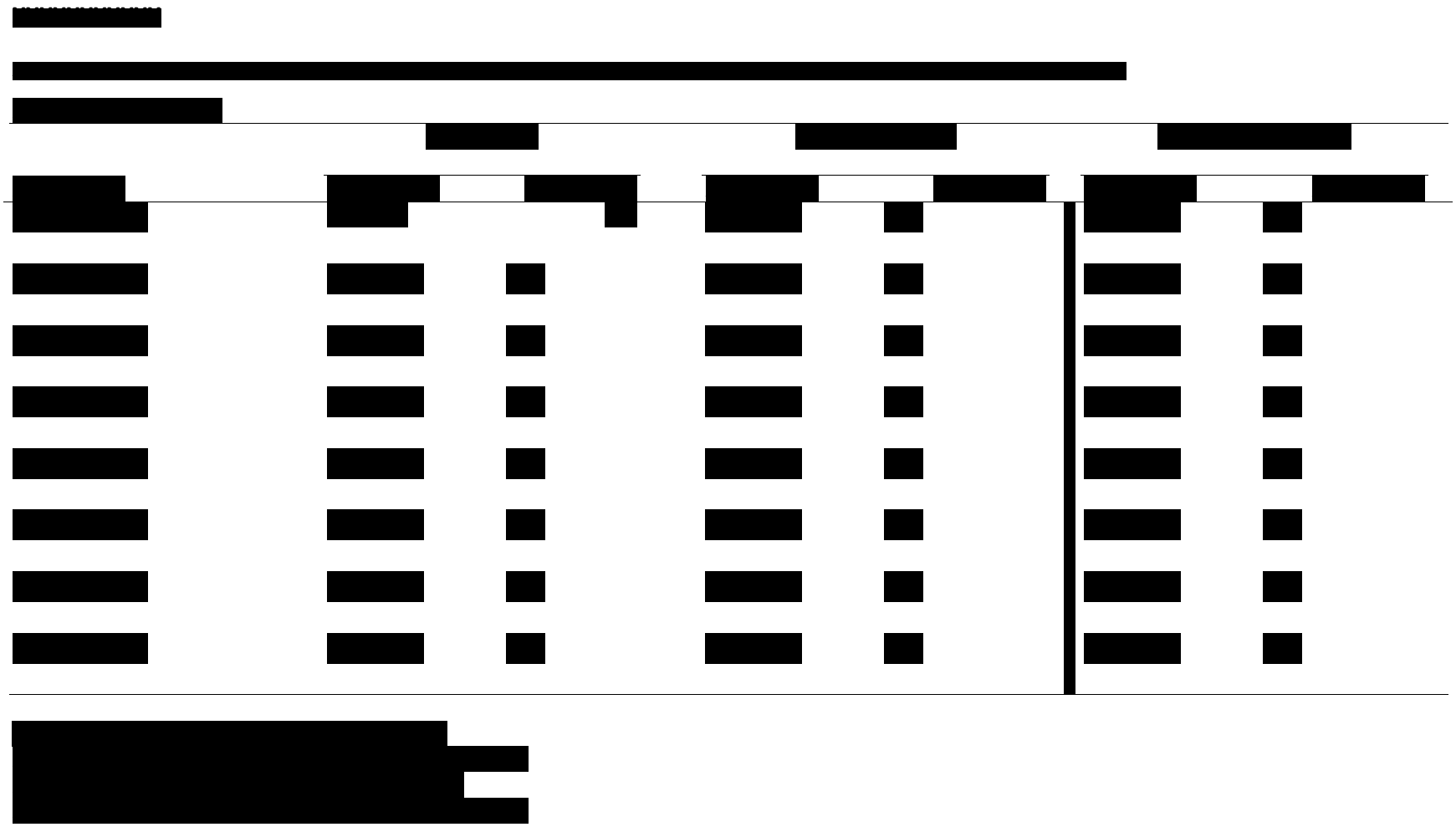
Minor bleed and minimal bleeding are not provided (there is no "minor" bleed designation; "minimal" bleeds were not adjudicated by CEC but only exist as downgrades from those considered possibly belonging to the primary safety outcome.) GI bleeds will be interpreted to mean Major bleeds with a site equal to gastrointestinal lower- or gastrointestinal upper-extremity.

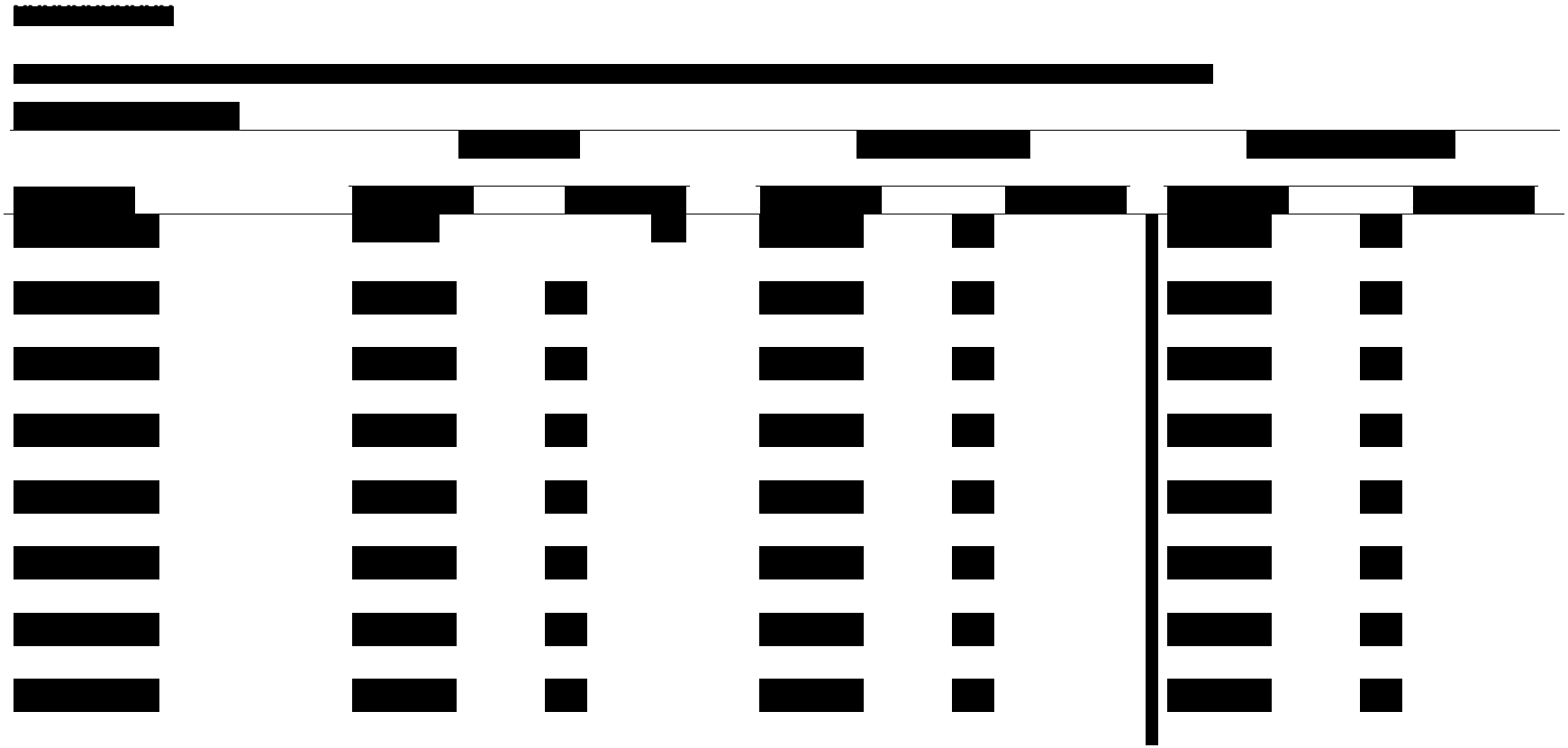
Subgroup d

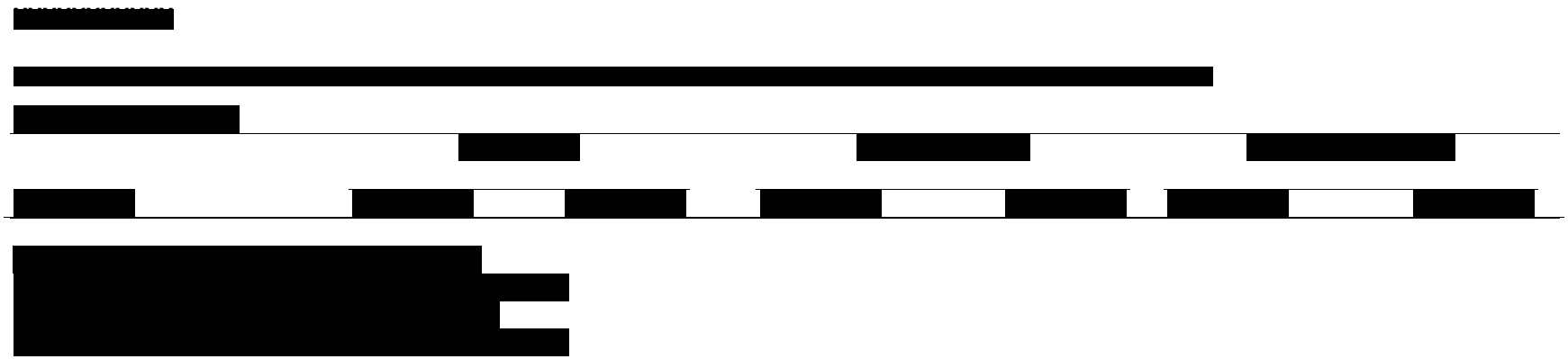
In line with the ERGs request, we have provided data based on individual patient TTR (<60%, ≥60%). However bias may be introduced by using such data as patients in each cohort would invariably have different baseline characteristics. As such, these are not randomised cohorts and data should be interpreted with caution. For this reason the data are marked as commercial in confidence.

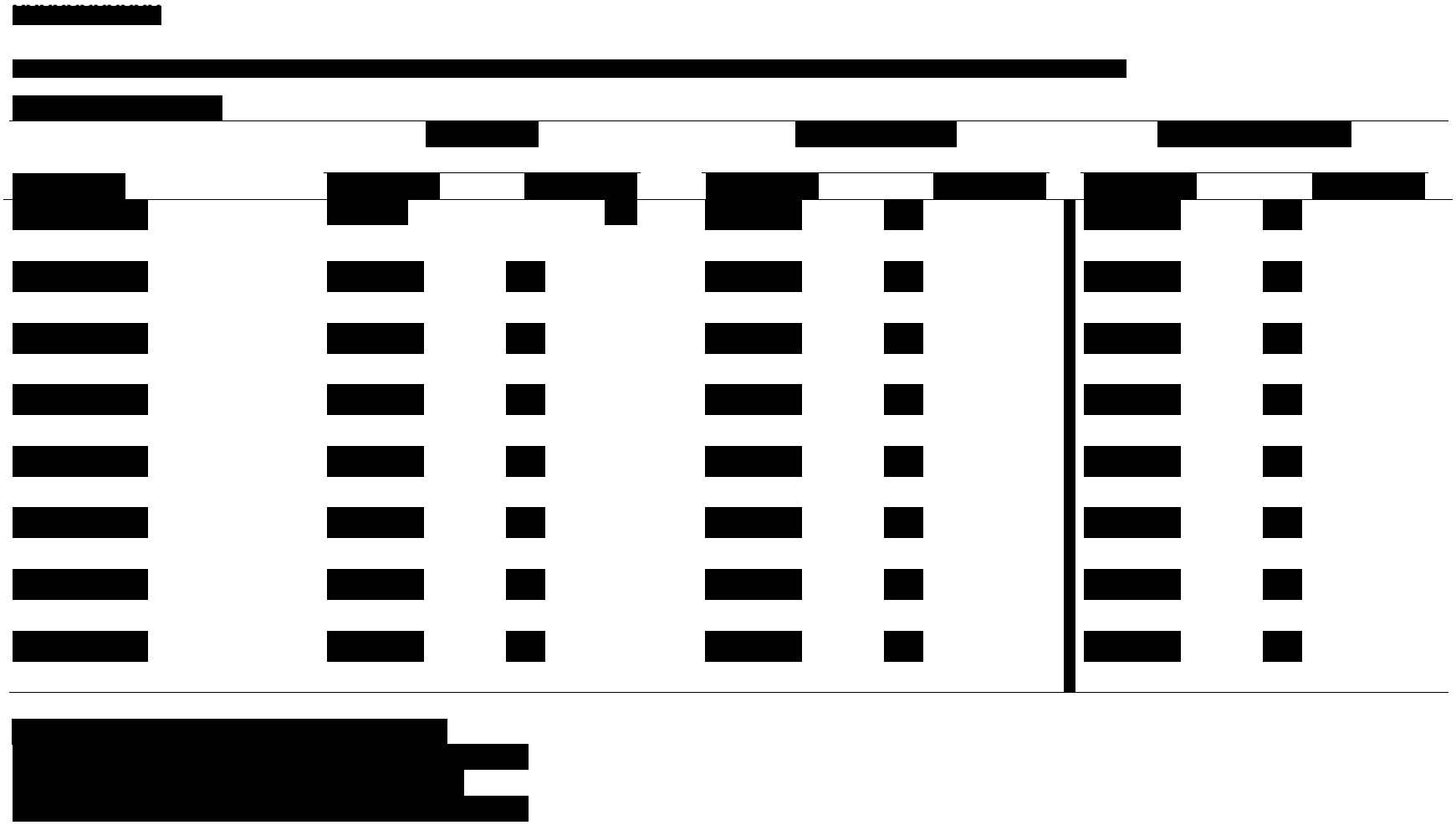
Imputed INR is calculated for the safety population on treatment using Point of Care device measurements. It is useful only for patients taking warfarin and thus it would not make sense to use off treatment data from the ITT population. In addition, the Point of Care device was not used in the off-treatment period. Therefore we feel it is not appropriate or relevant to provide this data.

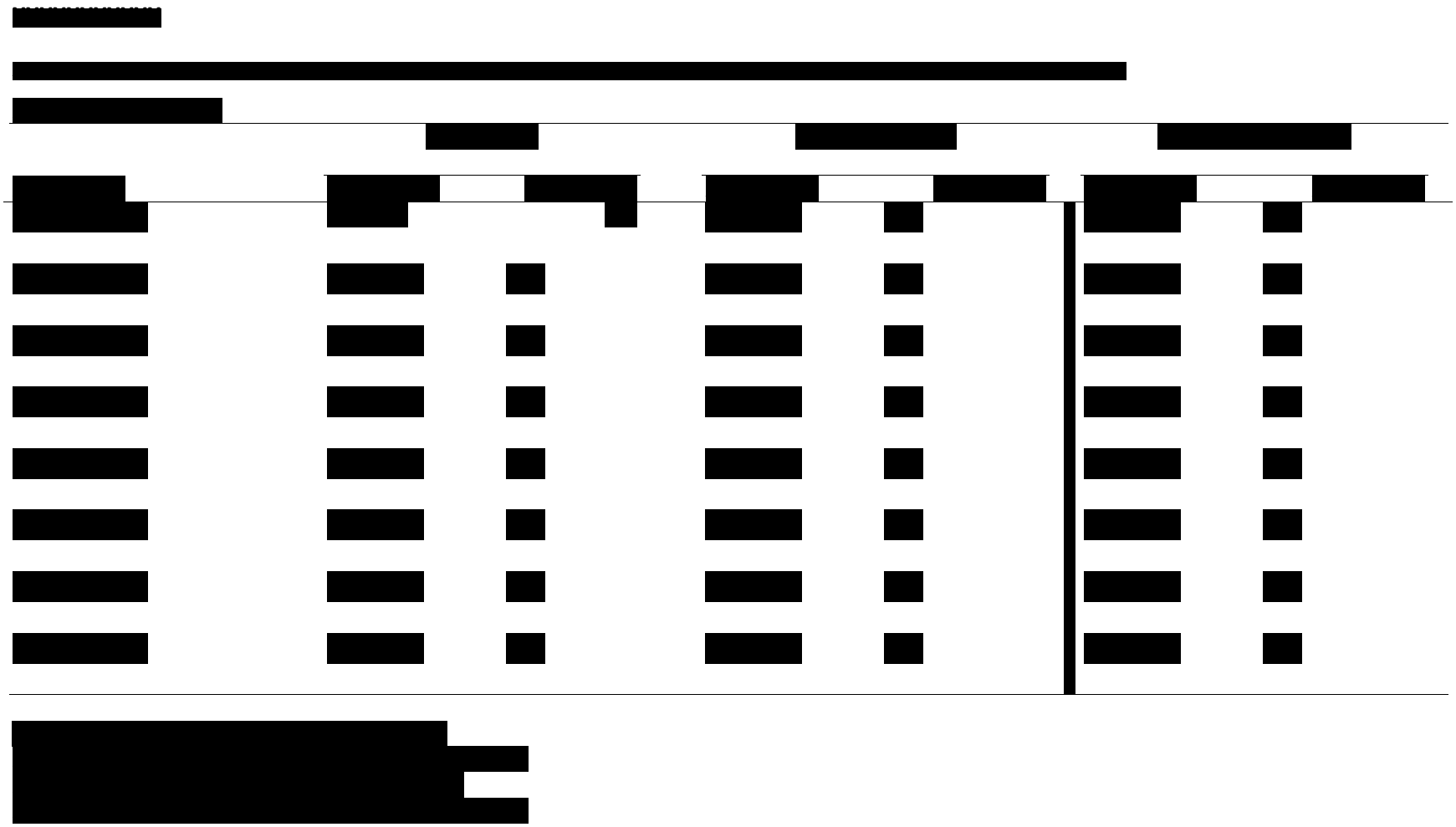


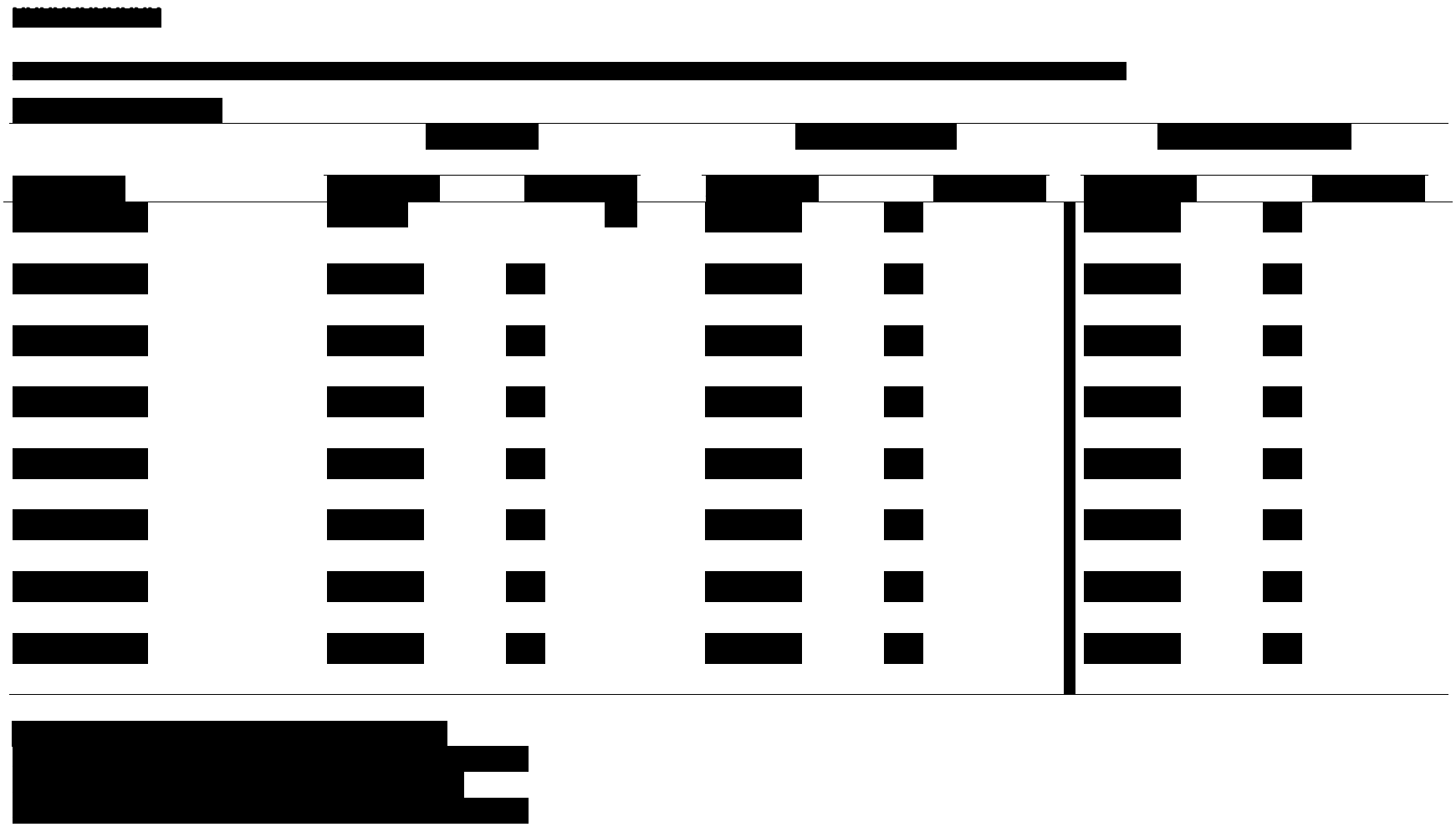


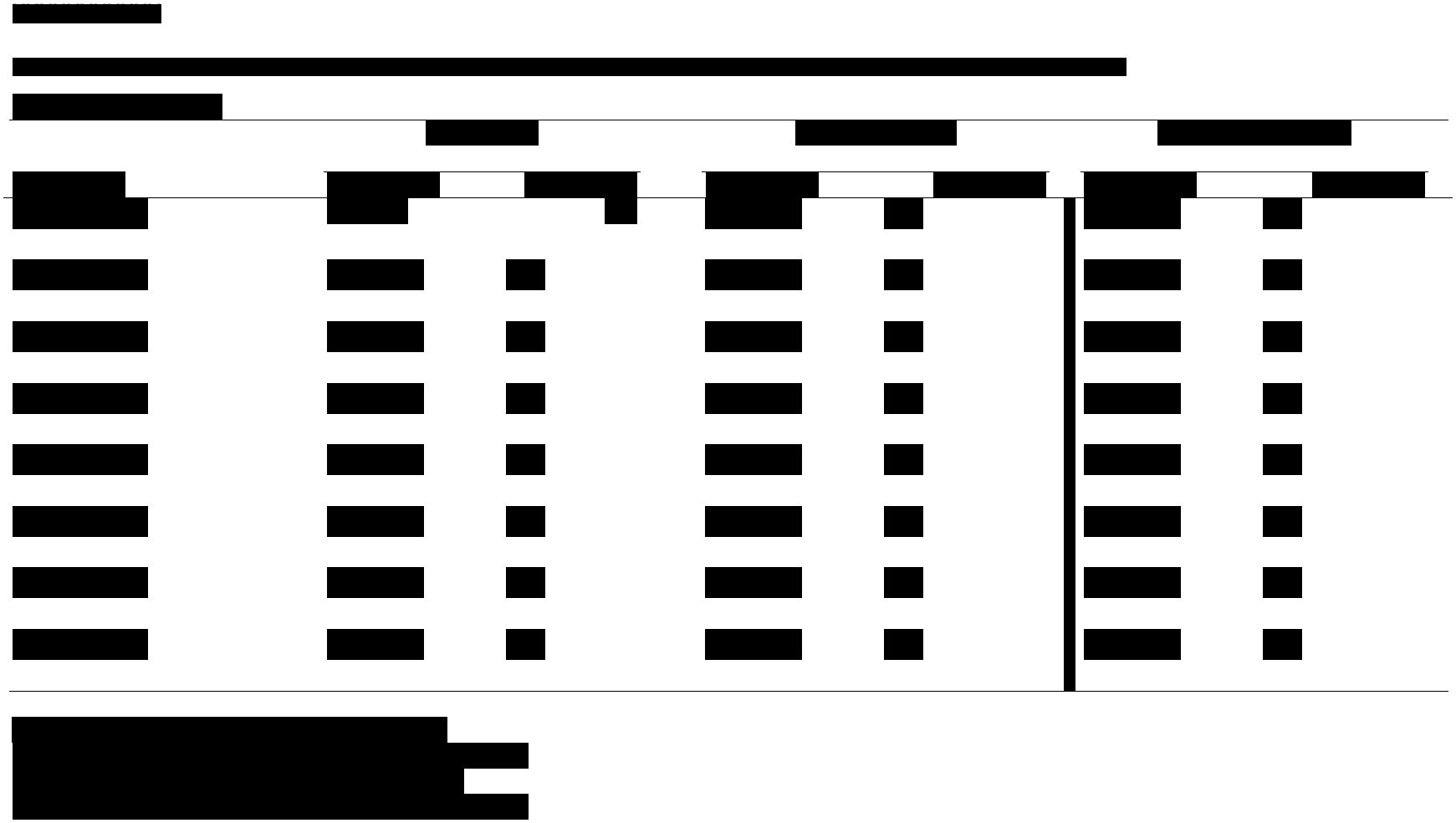


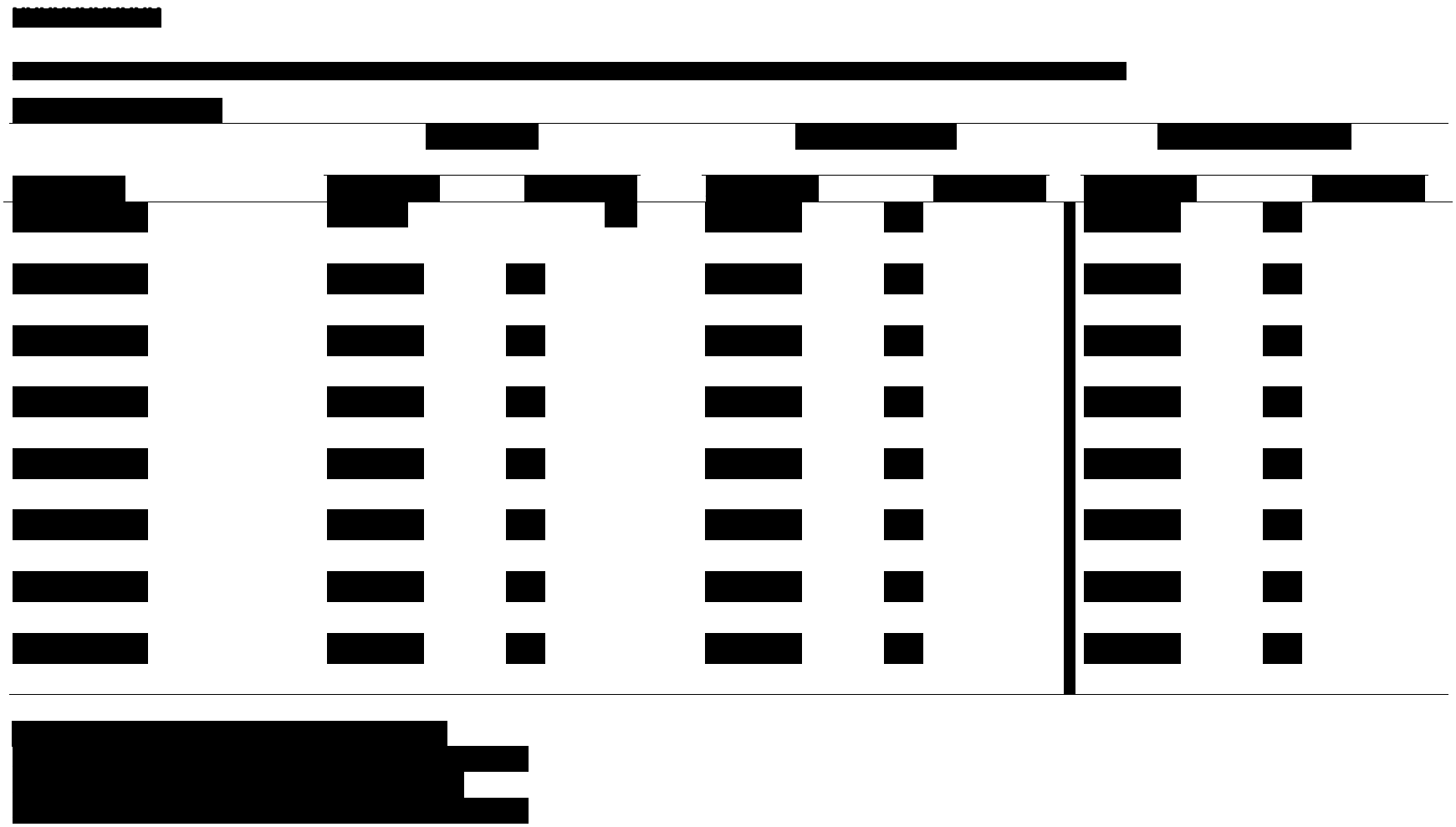


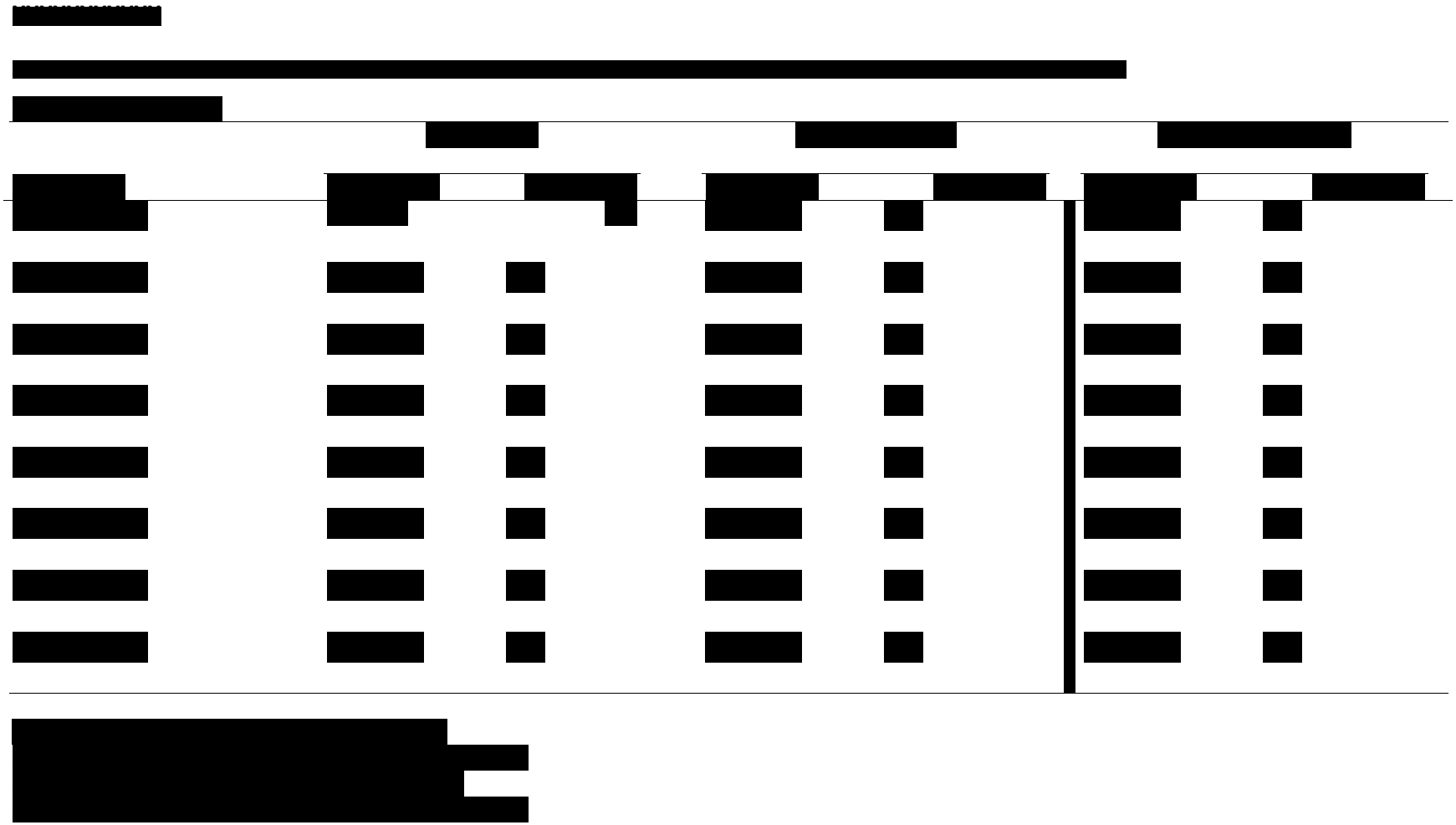


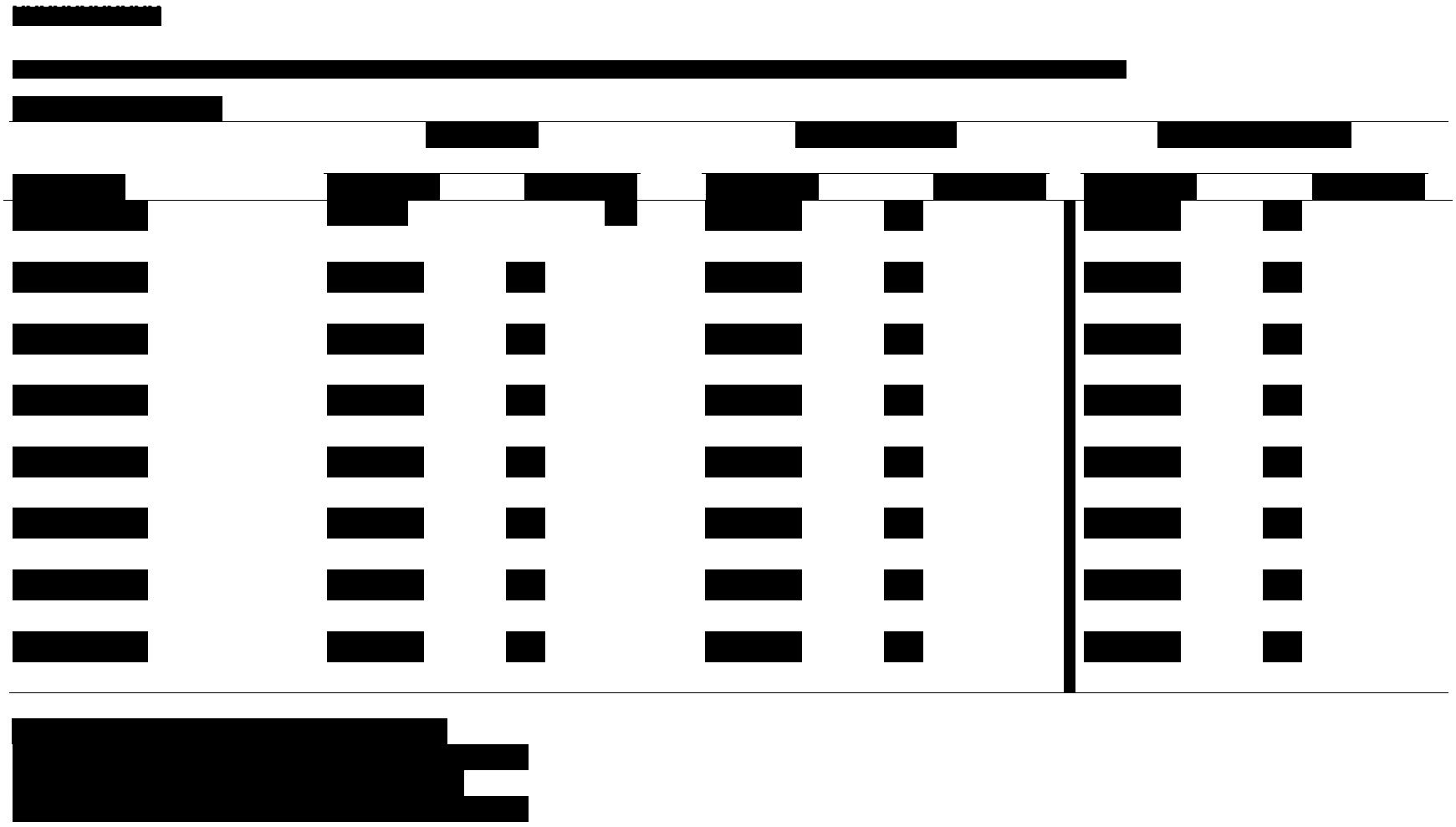


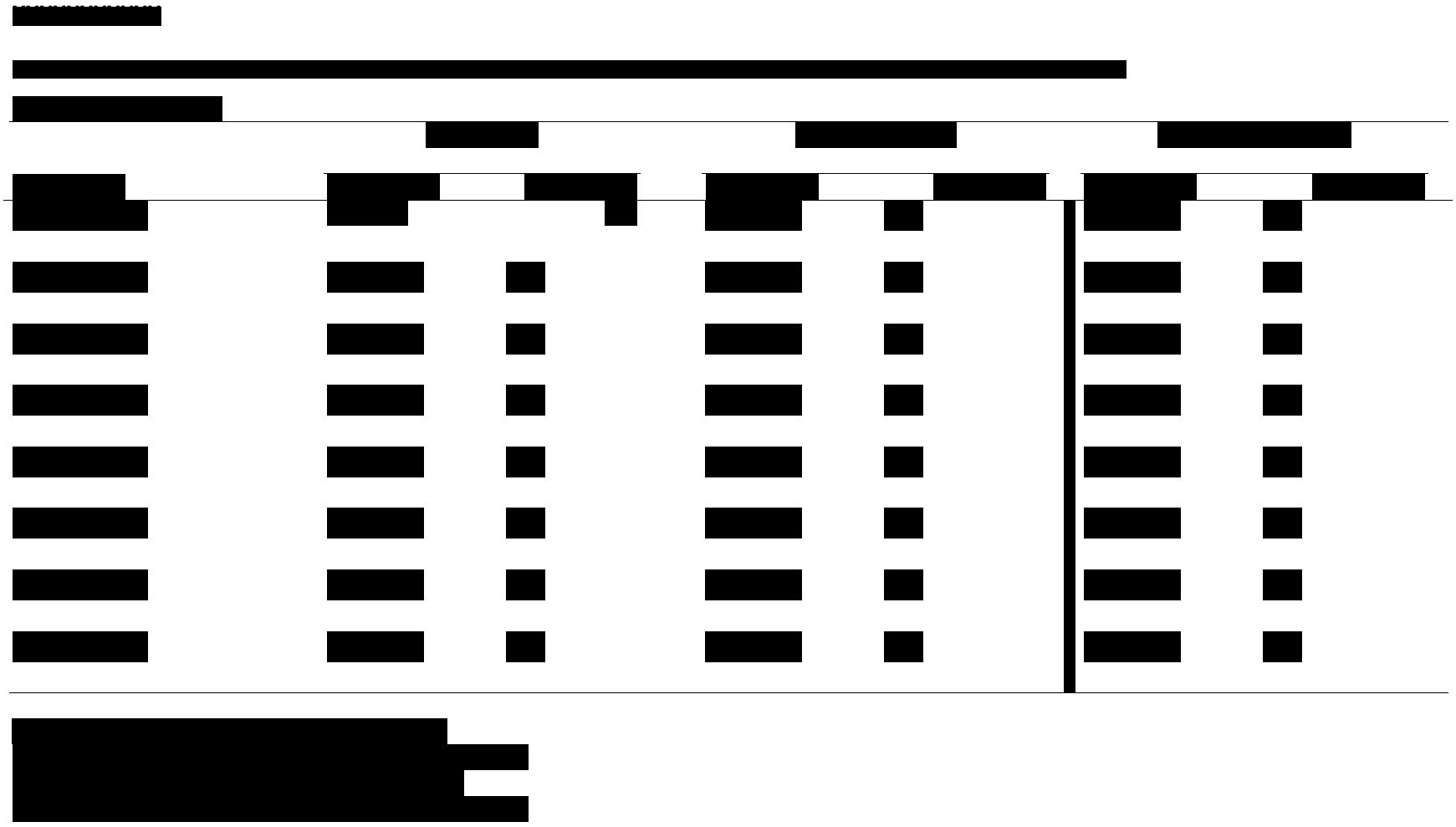


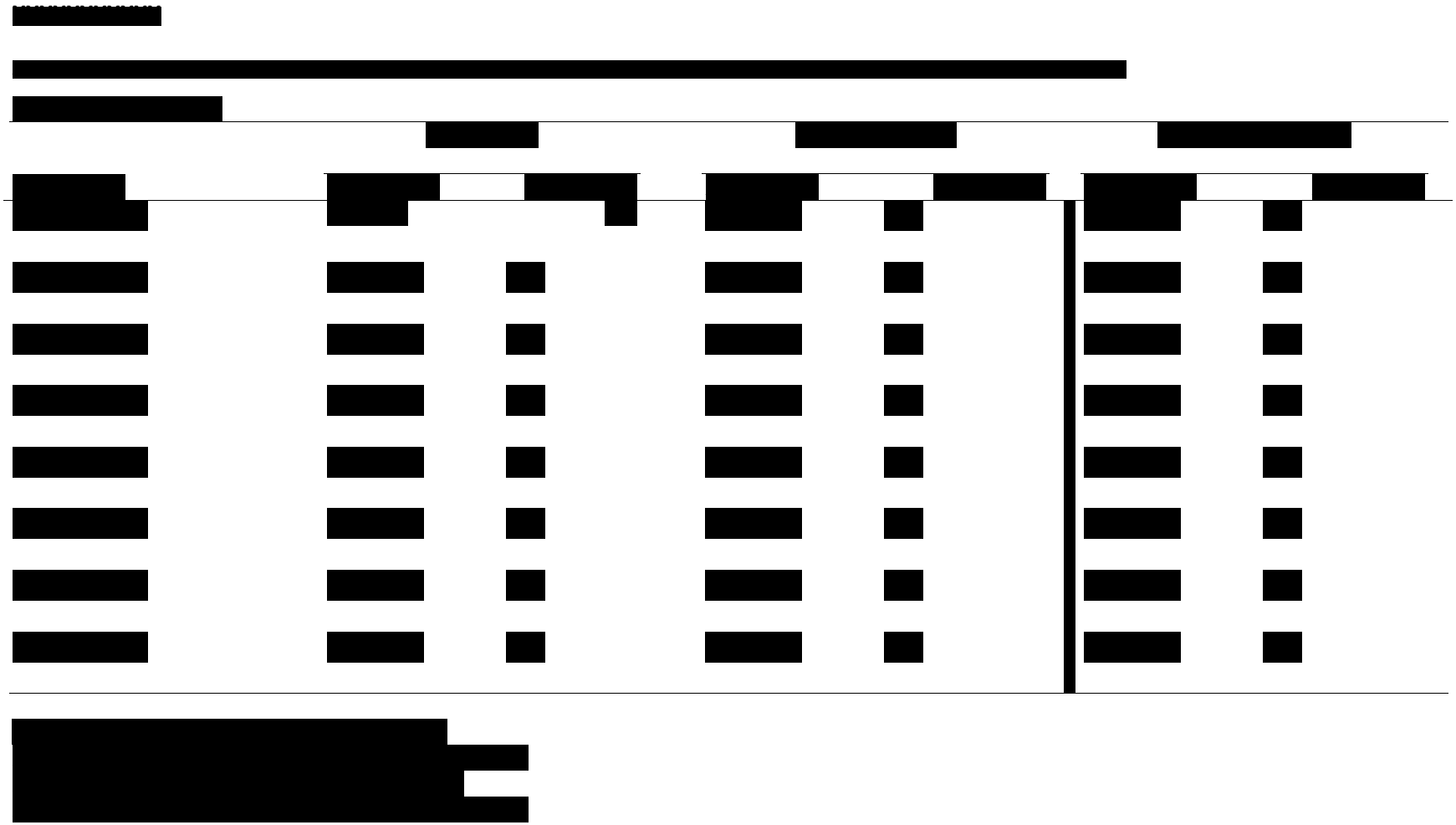


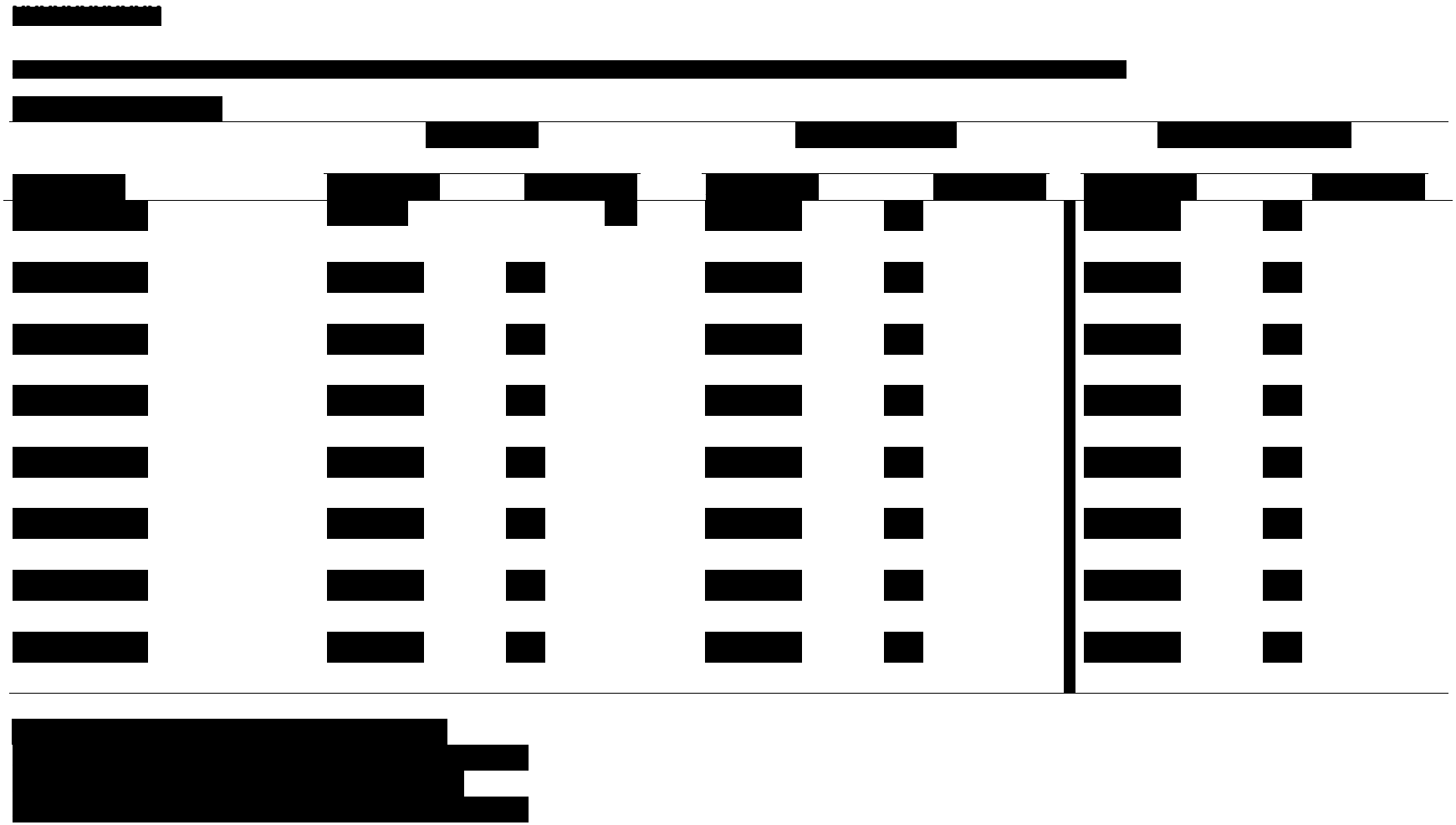


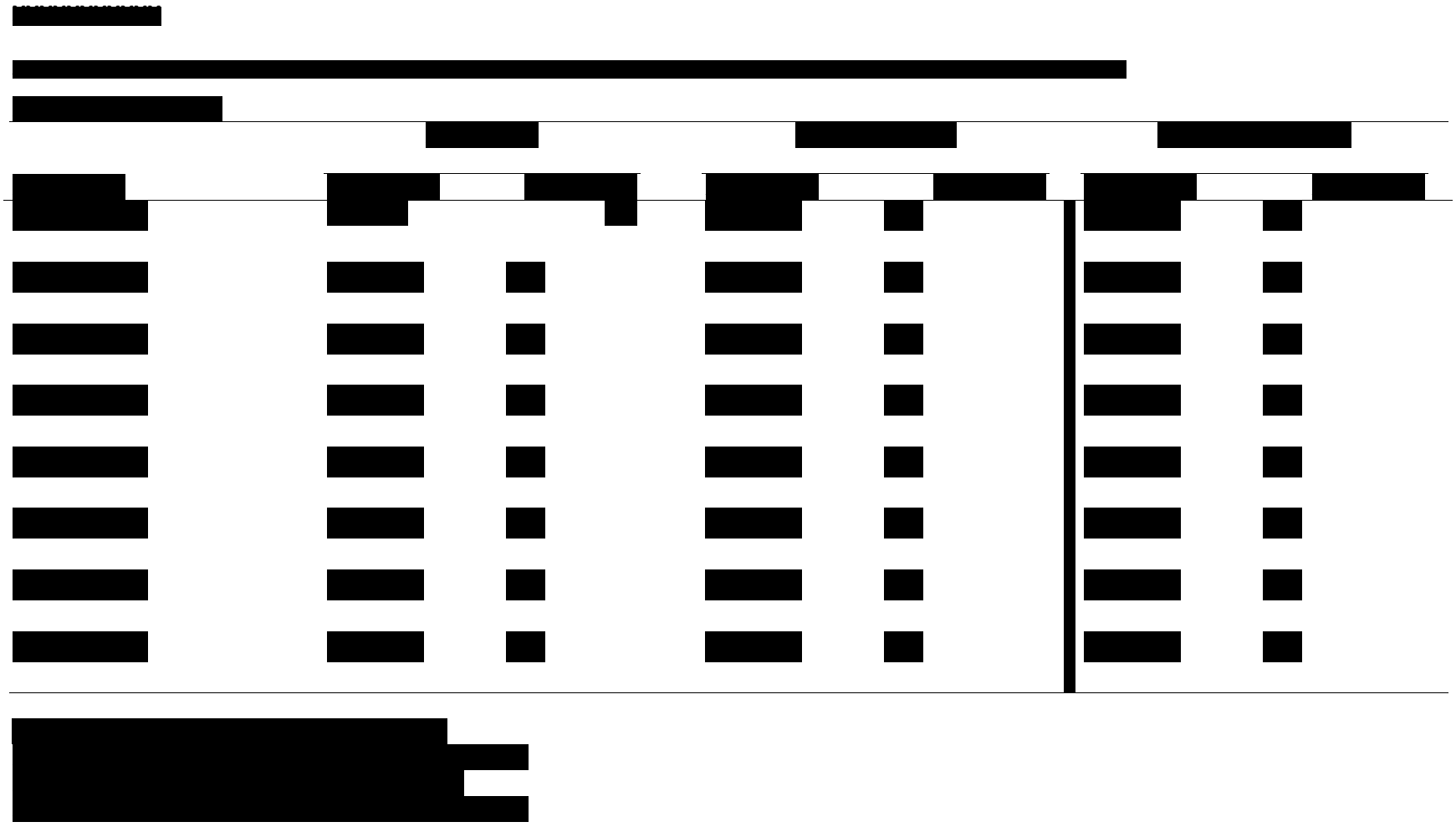


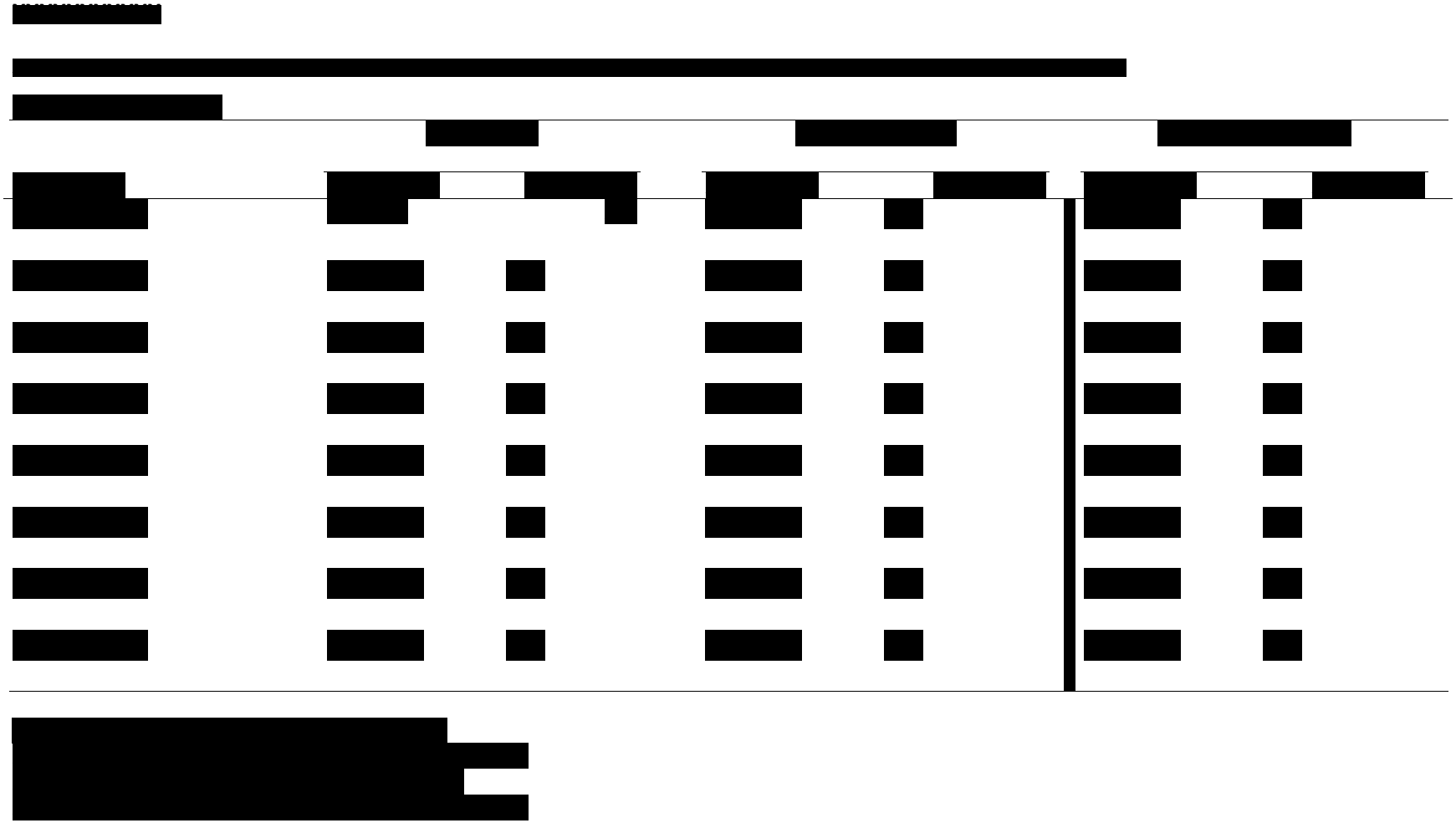


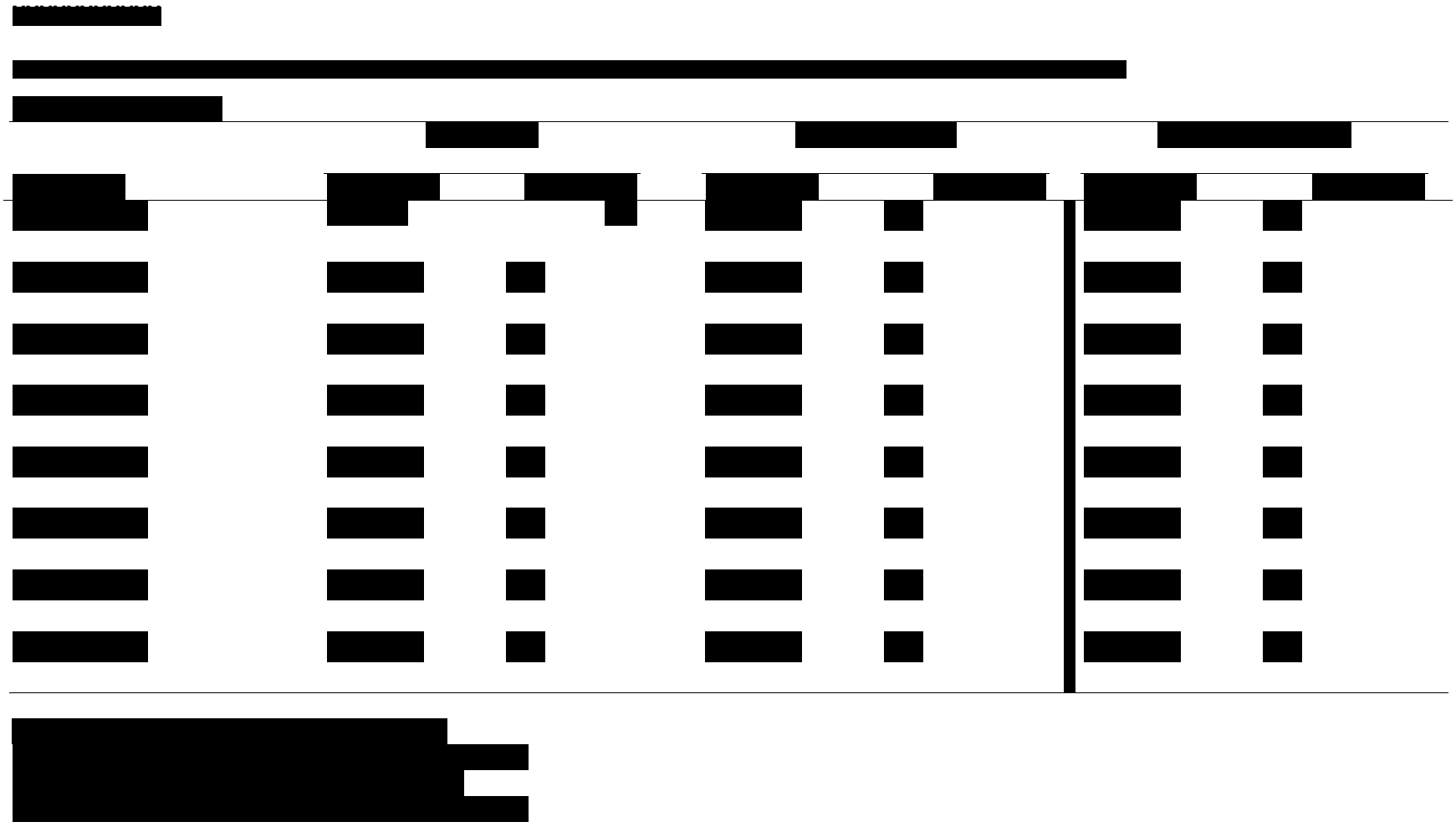


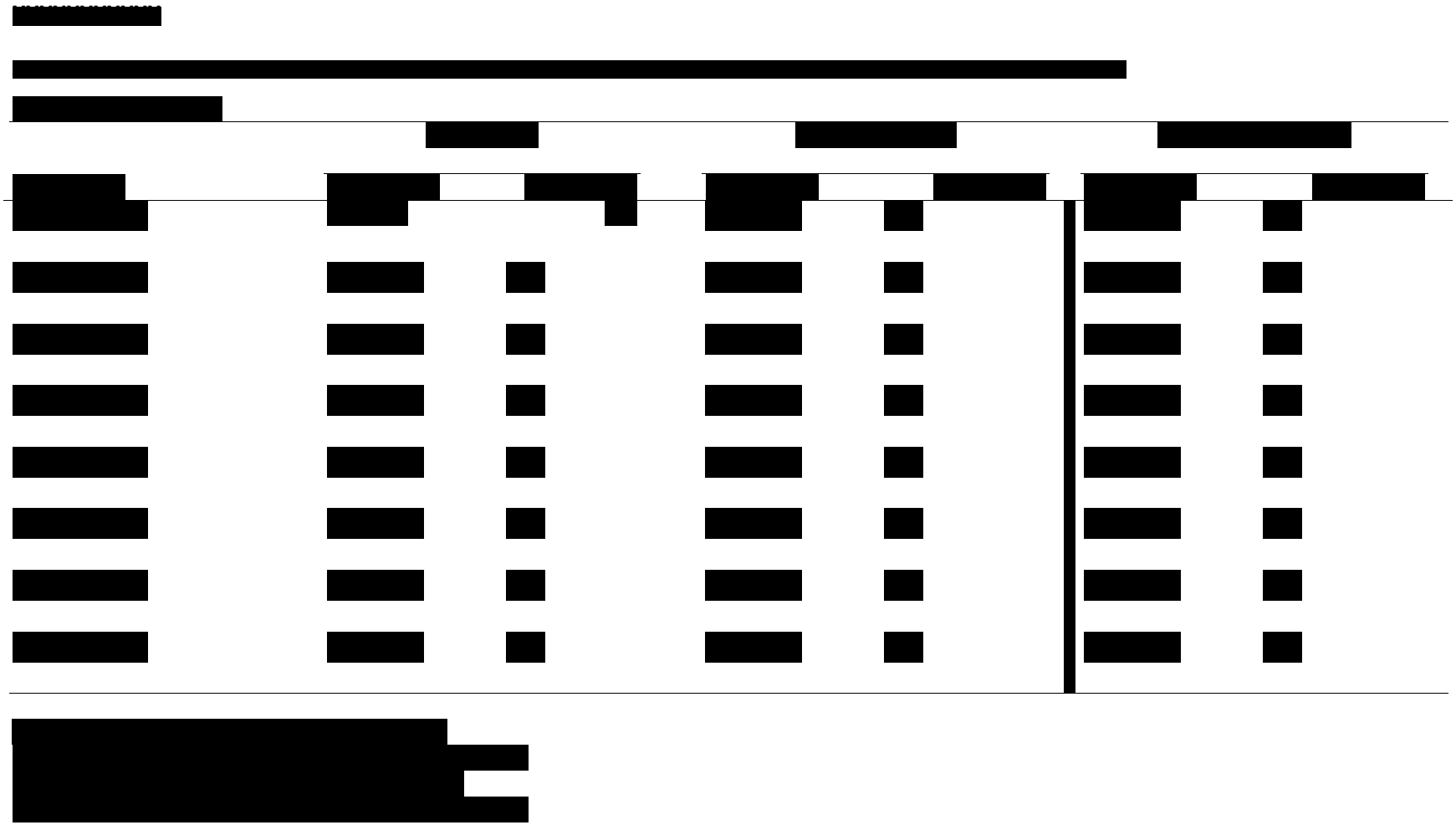


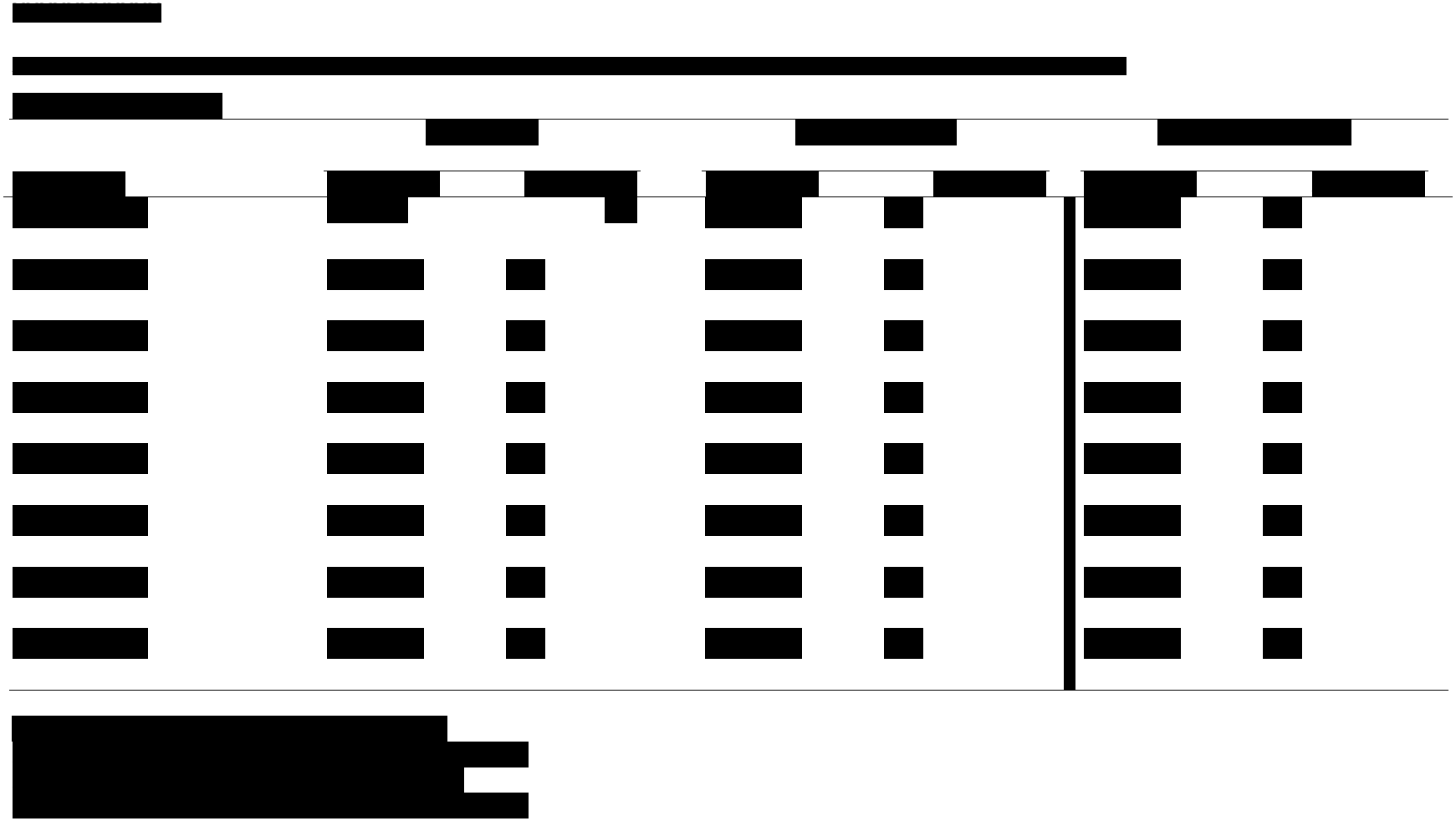


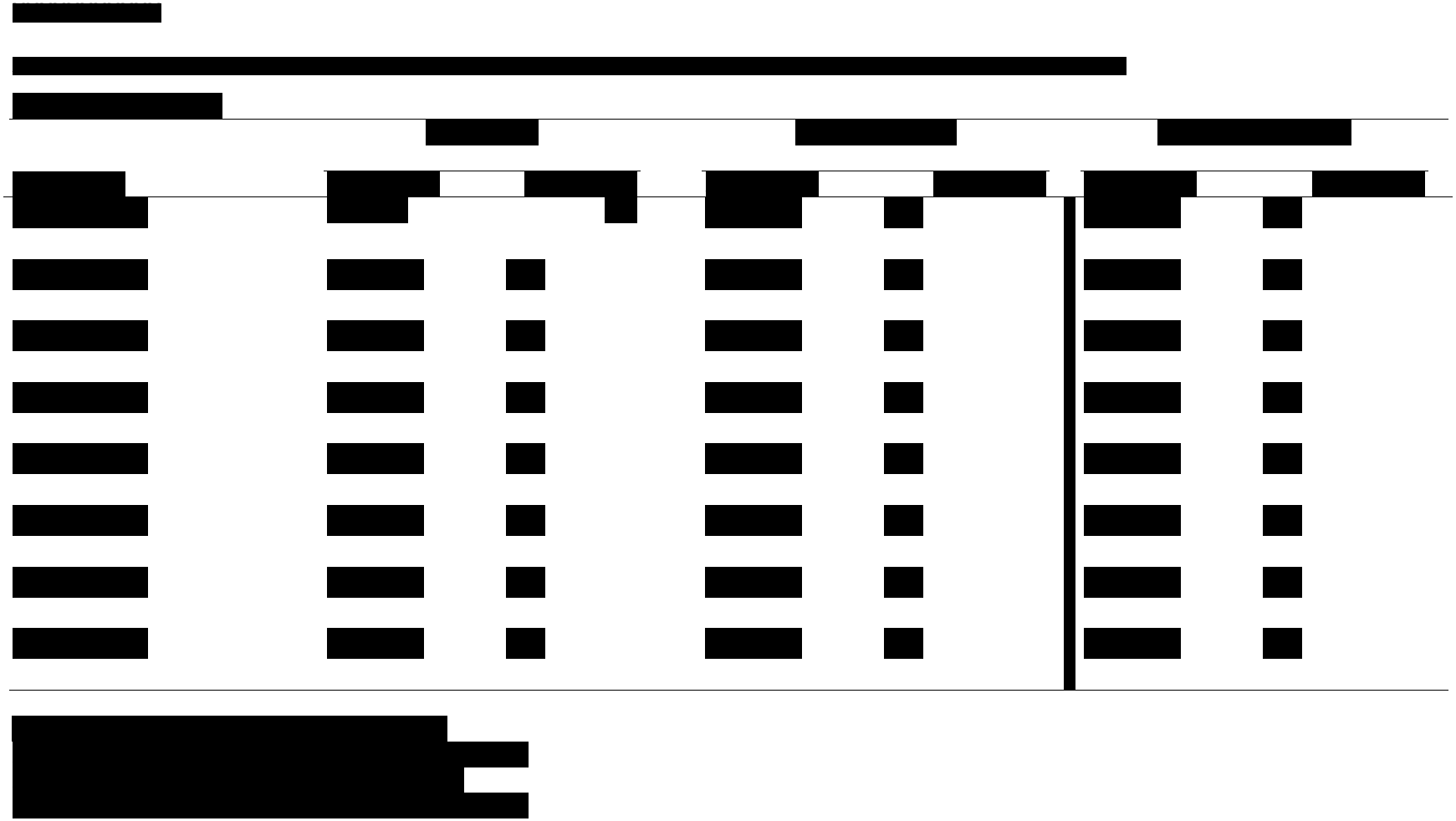


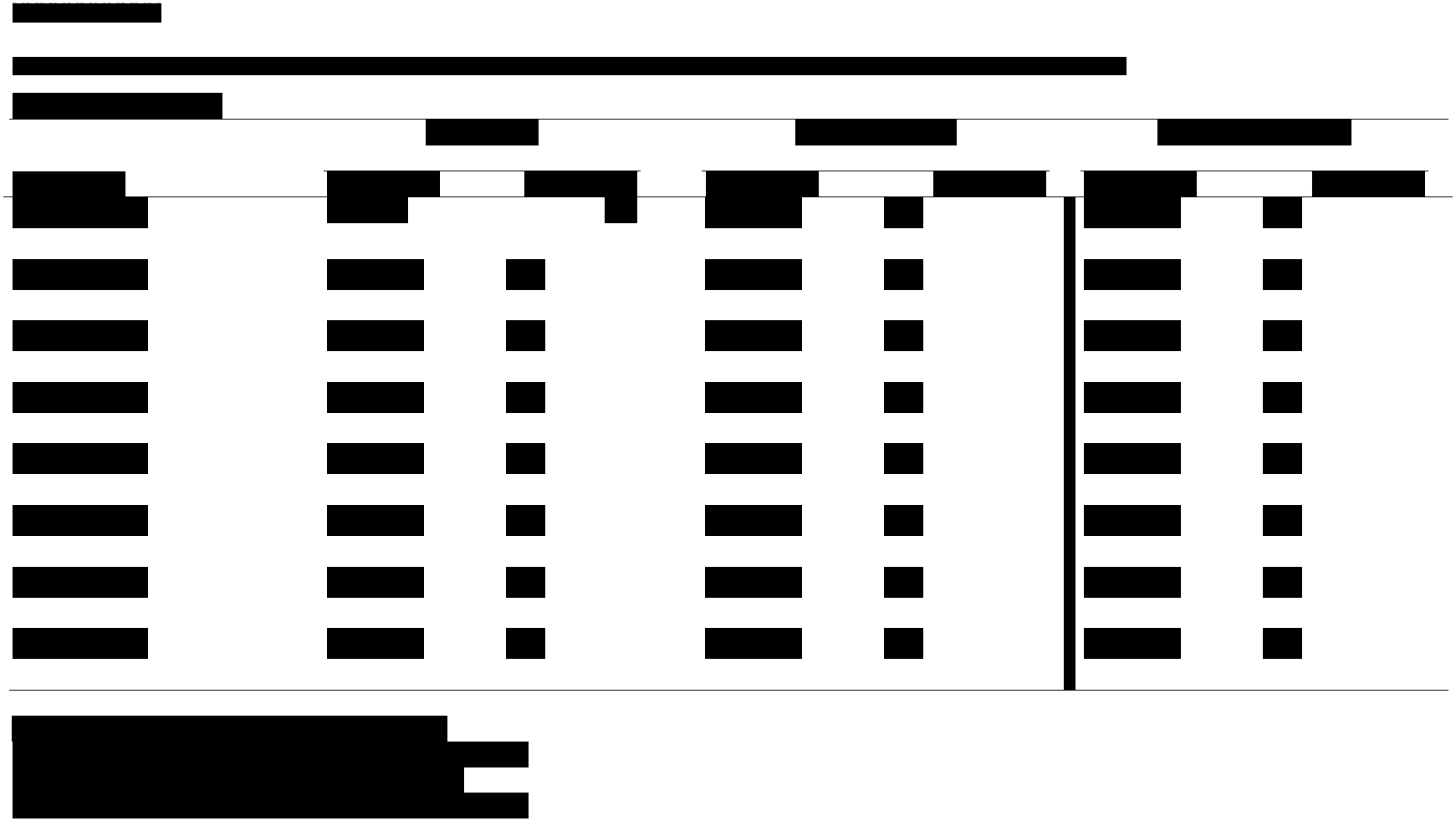


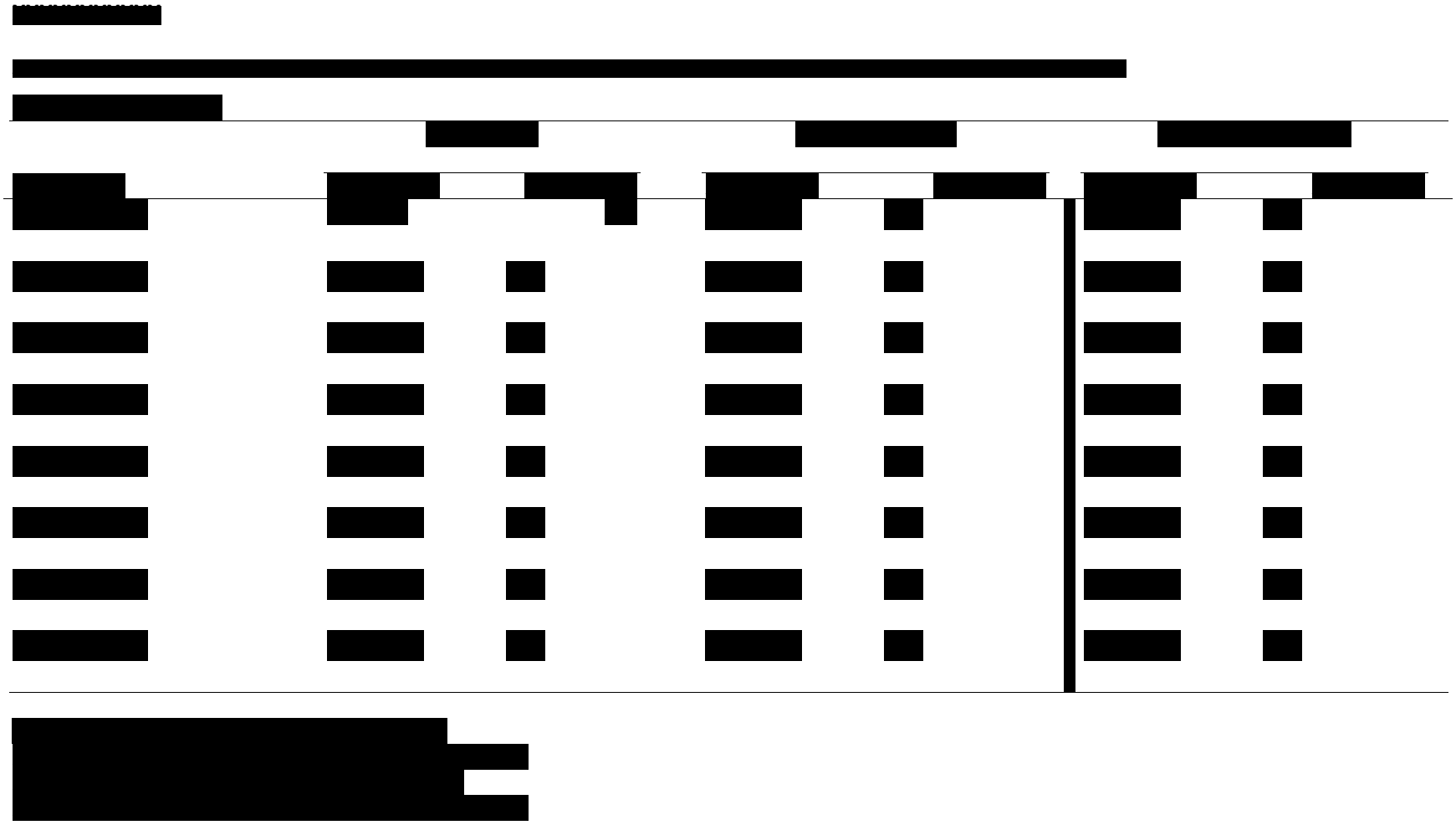




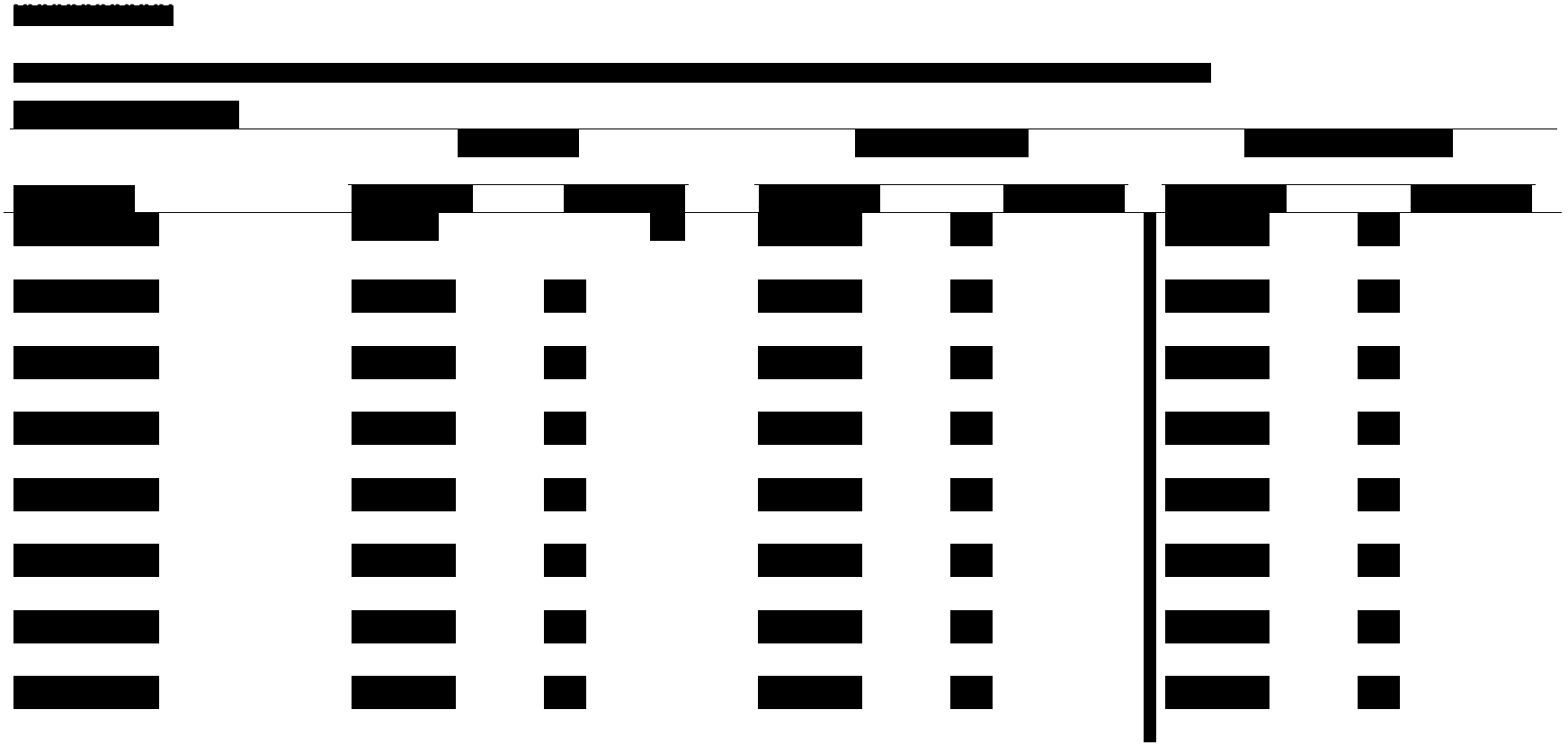


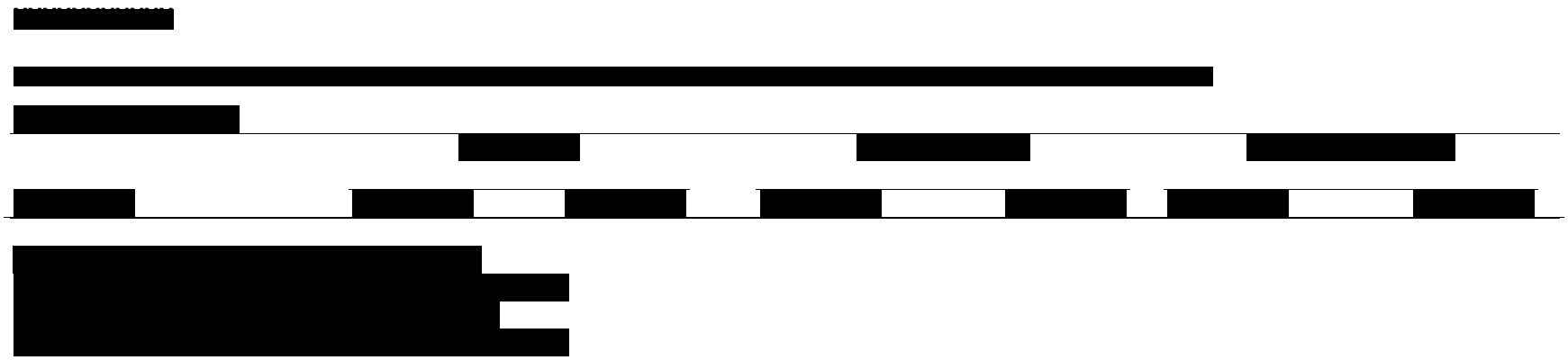


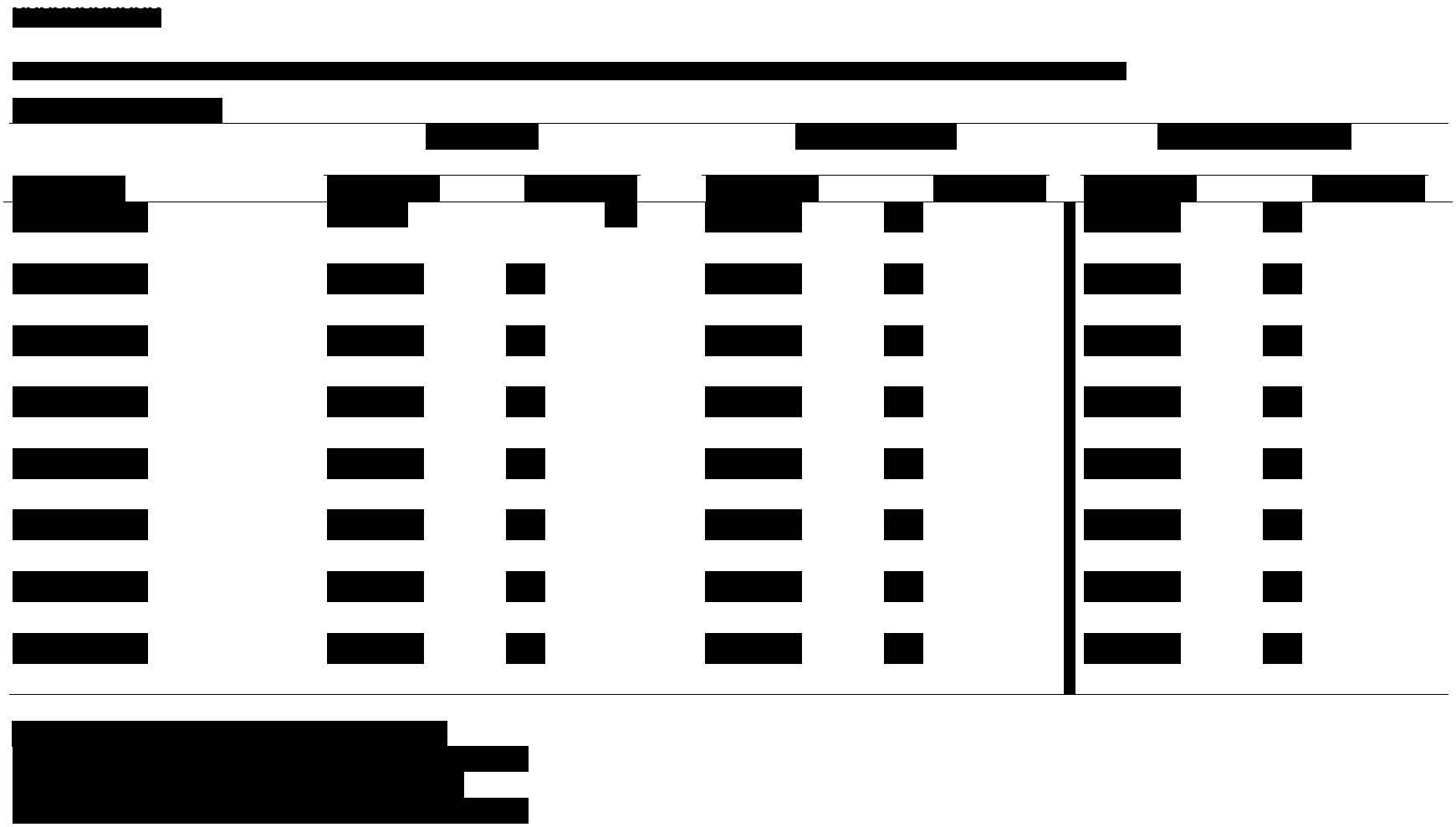


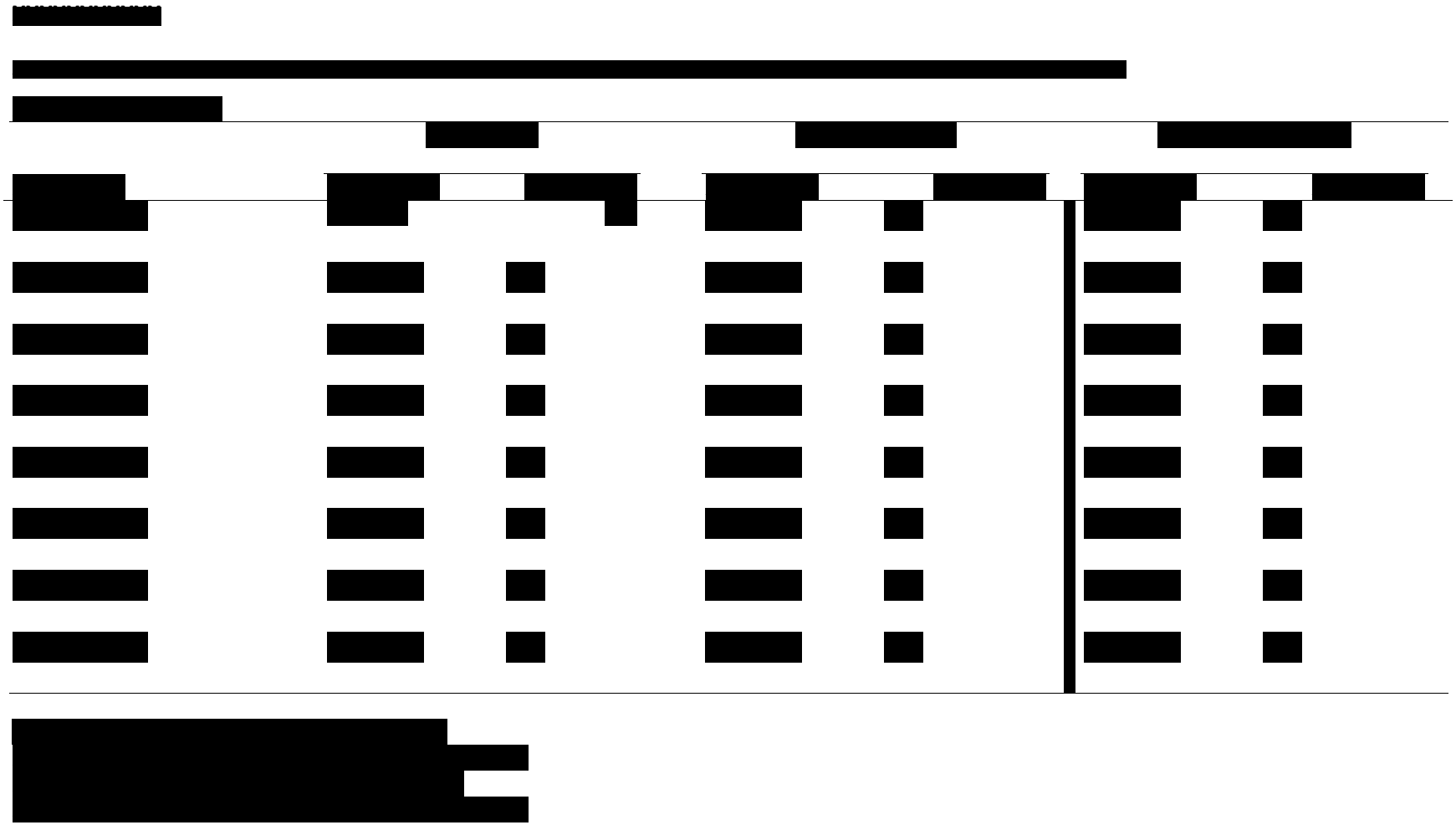


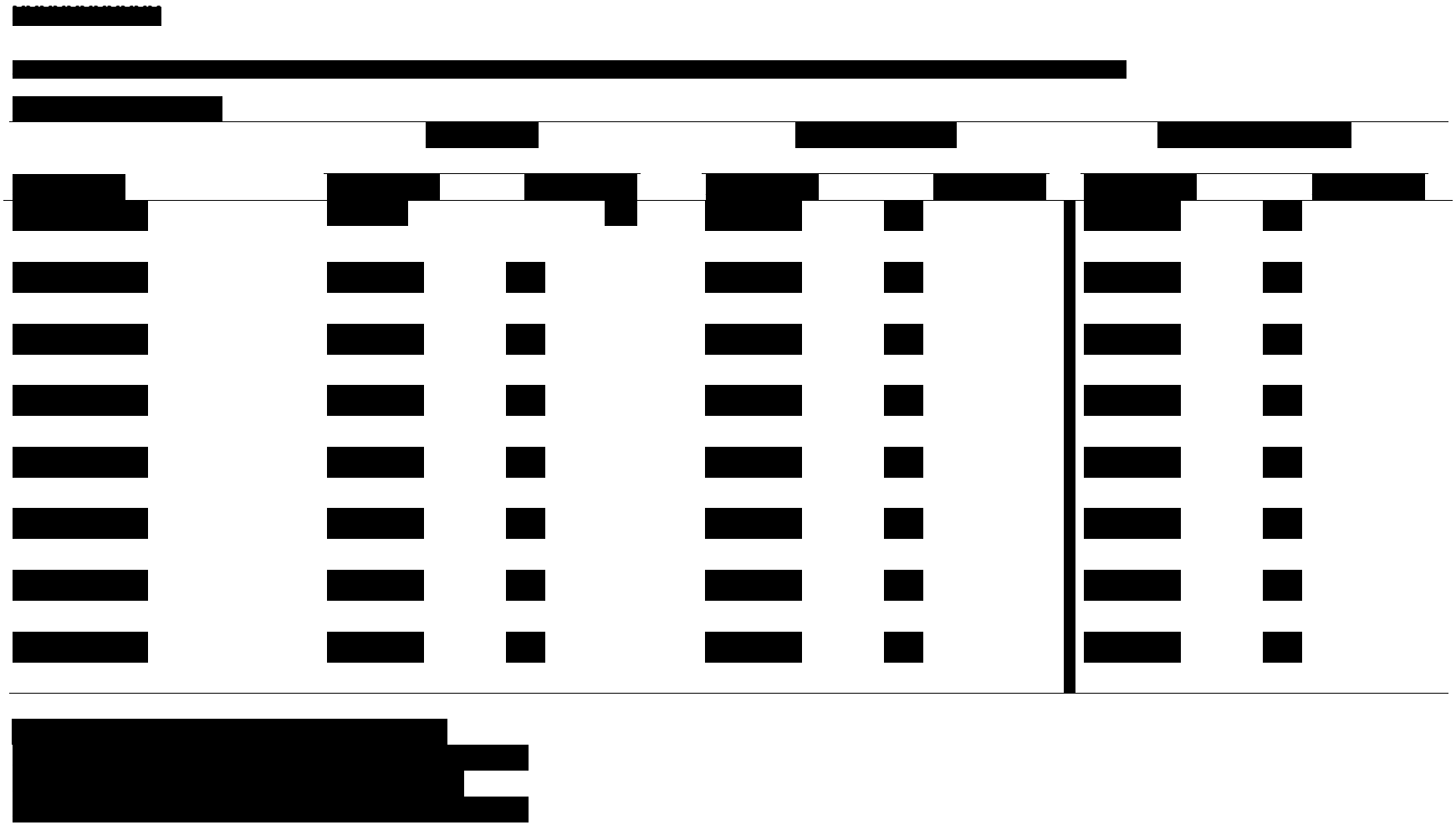
The analysis is provided as requested in the ITT population to site notification. It should be noted however that it is not suitable for inclusion in cost-effectiveness analysis as there was a median of 117 days off randomised treatment. Since rivaroxaban is not disease modifying, the effects of rivaroxaban would not be expected to carry-over into the post randomised treatment period. Therefore the effects of rivaroxaban are diluted due to the 117 days off randomised treatment and an analysis which considers the "on treatment" period (defined as on treatment plus two days) is appropriate.

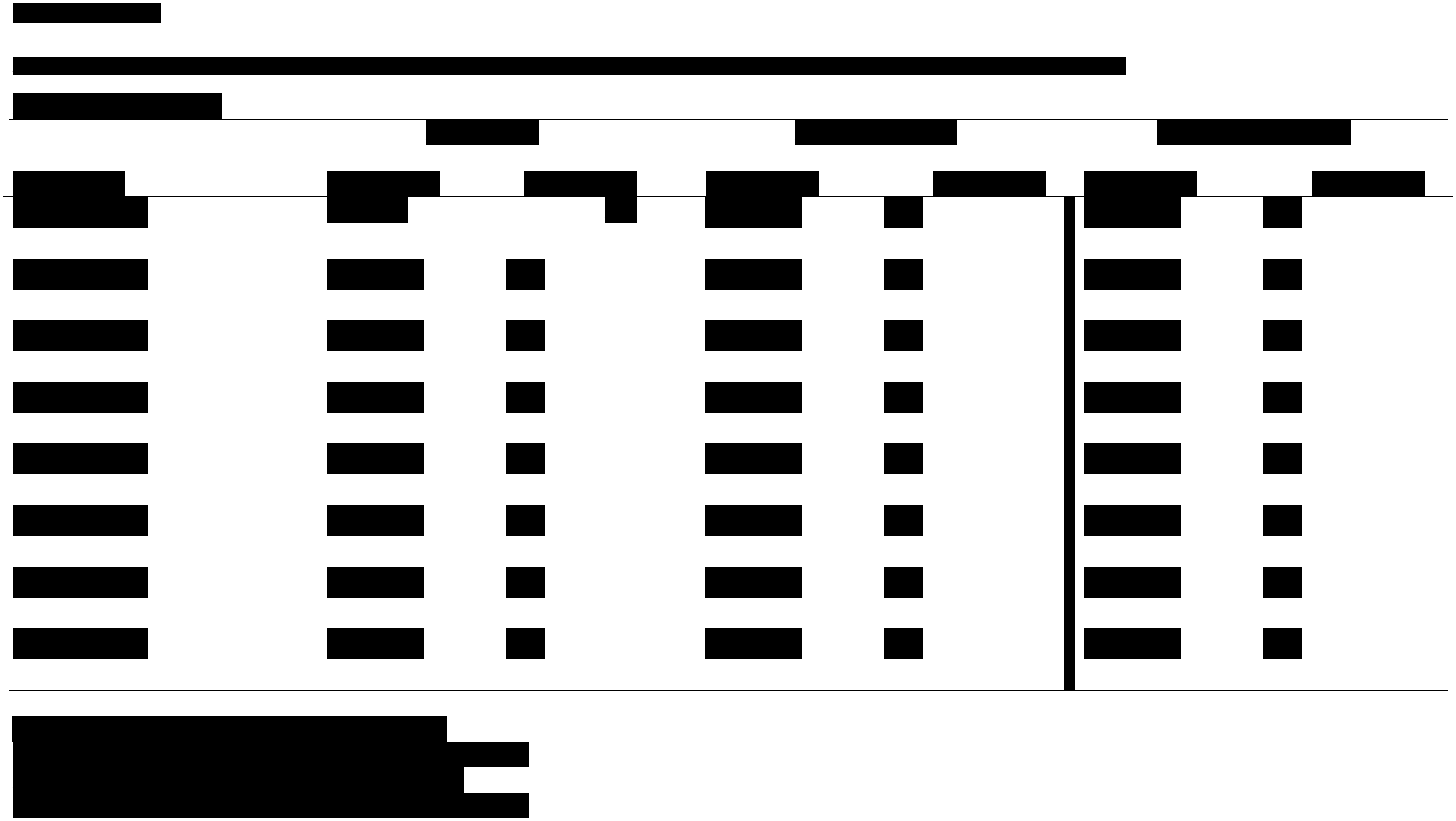












A27. On page 21 of the submission please clarify:

a. whether the proportion of patients with a CHADS2 score of zero is 12.6% of the total AF population or if this is specific to the non-valvular AF population.

This figure is referenced to the Gallagher 2008 paper *[Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? J Thromb Haemost 2008 Sep;6(9):1500-6.]*, where the study population consisted of patients aged 40 years or older with a diagnosis of chronic atrial fibrillation (cAF). Patients were excluded if they had a history of heart valve problems and/or valve replacement surgery. Therefore, the 12.6% refers to a population with chronic atrial fibrillation without a history of heart valve problems/ surgery – i.e. non-valvular.

b. why the estimated number of patients eligible for rivaroxaban is different in the text to that reported in table 8 (662,747 and 669,003).

Apologies – the number in the text is wrong. The number in table 8 is correct.

A28. In table 9 on page 32 of the MS, please confirm the criteria for determining whether people had chronic non-valvular AF for inclusion in the systematic review.

The criteria for determining whether the patients included in the studies had chronic non-valvular AF was based on the eligibility criteria reported in the publication.

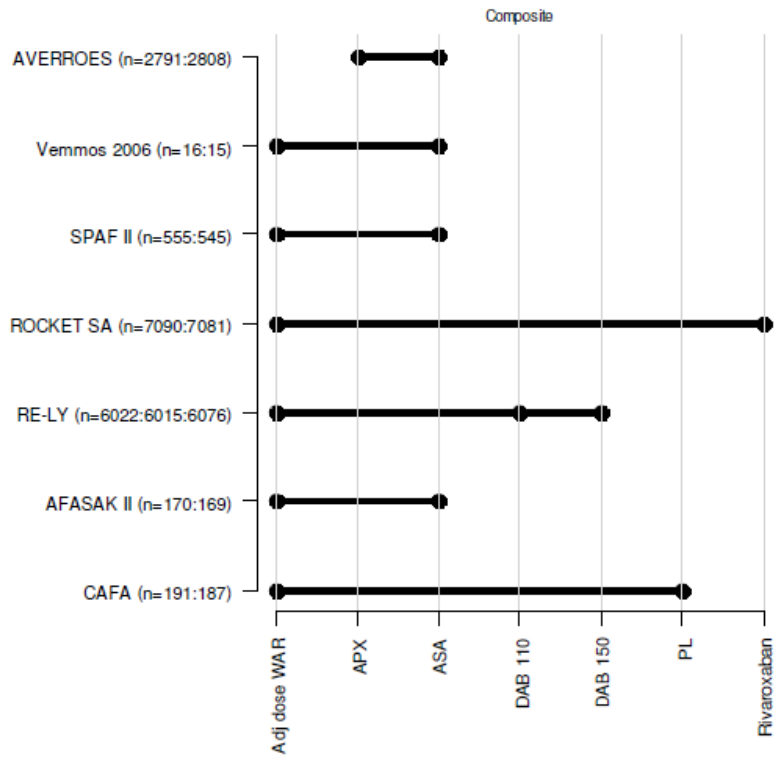
For the eligibility criteria, the systematic reviewers looked for a statement indicating patients with “non valvular” or “non-rheumatic” AF or the details of the inclusion/exclusion criteria indicating patients with non valvular AF.

Details of inclusion/exclusion criteria for each study are included in the systematic review report provided at the time of submission.

Please find attached the inclusion/exclusion criteria tables included in the report – attachment 4.

A29. Please provide network meta-analysis diagrams for the primary outcome using:

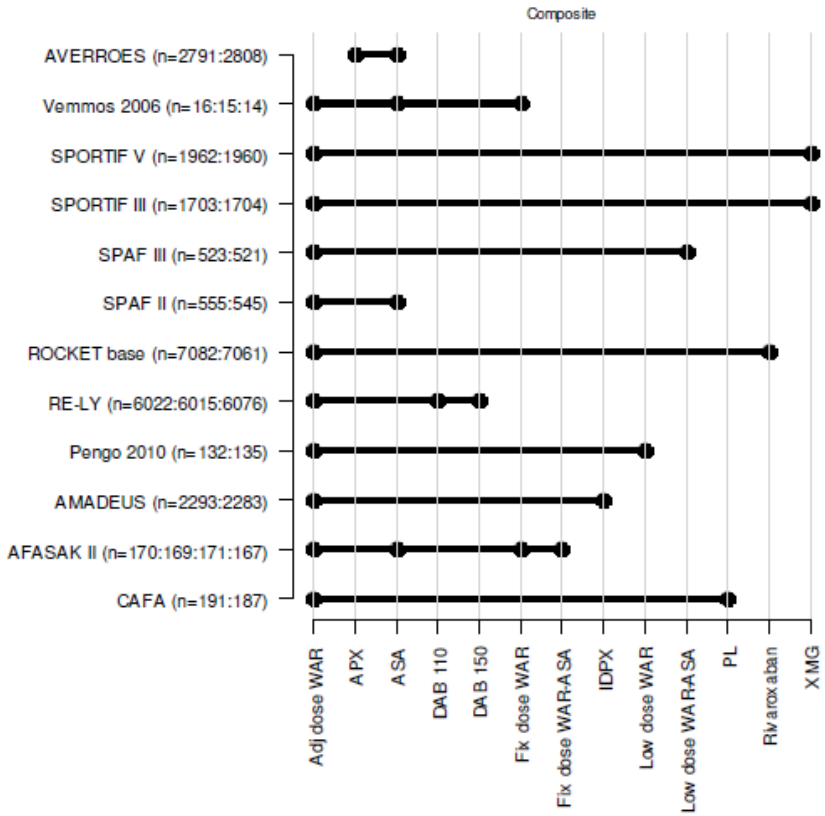
a. the ROCKET-AF ITT data and restricted set of comparator.



Network plot: Composite endpoint of ischaemic stroke or systemic embolism

b. the ROCKET-AF ITT data and full set of comparators.

Please note that the analysis for the full set of comparators using the ROCKET-AF ITT data was never conducted.



Network plot: Composite endpoint of ischaemic stroke or systemic embolism

A30. Please provide the data/risk of bias tables for RE-LY and Pengo 2010, as provided in the Appendices of the Oxford Outcomes report on the systematic review, for the other trials included in the systematic review and network meta-analysis.

Please see the table on the following page.

Study	Description of randomization	Description of allocation concealment	Blind treatment assignment	Description of pts. baseline characteristics and groups balanced	Analysis based on ITT	Adequacy of reporting of outcomes	Description of withdrawals/drop-outs
RE-LY Connolly et al, 2009 (1;2)	Adequate-computer generated	Adequate-Central randomization	Adequate for dabigatran dose groups. Warfarin group was not blinded. Outcome assessment was blinded	Adequate	Adequate	Adequate	Adequate- Follow up was achieved in 99.9% of patients. 20 pts. Were lost to follow-up.
Pengo et al 2010 (3)	Adequate-computer generated	Unclear	Adequate- Outcome assessment was blinded	Adequate	Adequate	Adequate	Adequate-40 patients withdrew from the study, reasons provided.

Reference List

(1) Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009 Sep 17;361(12):1139-51.

(2) Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009 May;157(5):805-10, 810.

(3) Pengo V, Cucchini U, Denas G, Davidson BL, Marzot F, Jose SP, et al. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. Thromb Haemost 2010 Feb;103(2):442-9.

A31. Please provide the following sensitivity analyses for all the outcomes reported in the network meta-analysis using the ITT restricted comparator data set:

a. restricting the VKA trial data included in the analysis to warfarin;

b. restricting the aspirin trial data included in the analysis to a mean daily aspirin dose of 150mg.

With these restrictions imposed the model becomes too unstable. The reduction in the number of studies included leads to some ratios being informed by a very small number of events with wide confidence intervals and the model becomes uninformative. For this reason these analyses are not presented here.

A32. Please provide details of any differences in the methods and trial inclusion/exclusion criteria between J-ROCKET and ROCKET-AF.

Key differences between the ROCKET AF and J-ROCKET AF are highlighted below.

Study objectives
The primary objective of the ROCKET AF trial was to compare the efficacy of rivaroxaban with dose-adjusted warfarin titrated to a target INR of 2.5 (range 2.0-3.0, inclusive) for the prevention of thromboembolic events in patients with non-valvular AF.

The J-ROCKET study was designed as a safety study. The primary aim of the J-ROCKET AF study was to evaluate the safety of rivaroxaban in Japanese patients with non-valvular AF, and to demonstrate that the safety of rivaroxaban was non-inferior to dose-adjusted warfarin, as assessed by the composite of major and non-major clinically relevant bleeding events. J-ROCKET AF was not powered to demonstrate non-inferiority in efficacy.

The J-ROCKET AF study was similar in design to ROCKET AF study. It was a prospective, randomised, double-blind, double-dummy, parallel-group, active-controlled multicentre study.

Sample size
Number of randomised subjects in ROCKET AF – 14,264 (ITT)
Number of randomised subjects in J ROCKET AF – 1,280 (ITT), 1,278 (safety analysis)

Inclusion/ exclusion criteria
The inclusion and exclusion criteria of J-ROCKET AF were mainly similar to those of ROCKET AF. The main differences in the inclusion criteria were that J-ROCKET AF only recruited patients of Japanese ethnicity, the minimum age for inclusion was ≥20 years in J-Rocket AF, compared with ≥18 years in ROCKET AF.

Rivaroxaban dose used
In J-ROCKET AF the 15mg daily dose of rivaroxaban for non-renally impaired patients is lower than the 20mg daily used in the ROCKET AF study to reflect the prevailing anticoagulant guidelines in Japan (INR target range for Japanese patients ≥ 70 years 1.6–2.6 compared to a standard INR target of 2.0−3.0 in global guidelines) – reflecting the specific characteristics of the patient population in Japan and local medical practice. 10 mg was given to subjects with CrCl of 30−49 ml/min, inclusive.

Target INR range for the warfarin treatment group

In ROCKET AF - Warfarin: adjusted dose with INR target 2.5 (range 2.0-3.0) for all subjects.

In J ROCKET AF - Warfarin: adjusted dose with INR target range 2.0-3.0 for subjects <70 yrs and 1.6-2.6 for subjects ≥70 yrs

Statistical analysis

The primary safety endpoint was the composite of major and non-major clinically relevant bleeding events, and the primary safety analysis was based on "on-treatment" data from the safety population.

A33. Please provide the ITT, per protocol and safety on treatment data for each of the primary, secondary and safety outcomes in J-ROCKET.

The J-ROCKET study was designed as a safety study. The primary safety endpoint was the composite of major and non-major clinically relevant bleeding events, and the primary safety analysis was based on "on-treatment" data from the safety population. J-ROCKET AF was not powered to demonstrate non-inferiority in efficacy.

The safety analysis included 1,278 (639 in each group) who received at least one dose of study medication.

The rate of the primary safety endpoint was 18.04 per 100 patient-years in the rivaroxaban group and 16.42 per 100 patient-years in the warfarin group (HR 1.11, 95% CI [redacted]) demonstrating non-inferiority of rivaroxaban to warfarin.

Similar results were demonstrated for non-major clinically relevant bleeding events between the rivaroxaban group ([redacted]) and the warfarin group ([redacted]).

Importantly, there were fewer intracranial haemorrhages in the rivaroxaban groups ([redacted] rivaroxaban patients ([redacted]) versus 10 warfarin patients ([redacted]) as reported in the table below.

Table: Safety outcomes: bleeding rates in J-ROCKET AF

Endpoints	Rivaroxaban (N=639)		Warfarin (N=639)		Rivaroxaban vs. Warfarin
	Total, n	Event rate (100 pt-yr)	Total, n	Event rate (100 pt-yr)	Hazard Ratio (95% CI)
Composite major and non-major clinically relevant bleeding n (%)	138	18.04	124	16.42	1.11 ([redacted])
Major bleeding, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin/haematocrit drop#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transfusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Critical organ bleeding**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatal bleeding	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-major clinically relevant bleeding, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Haemoglobin/haematocrit drop=a fall in haemoglobin ≥2 g/dl.

**Critical bleeding sites included: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneum

NS – Not stated

The primary efficacy endpoint was the composite of adjudicated stroke and non-CNS systemic embolism. Regarding results for the primary efficacy endpoint up to 2 days after the last dose for the PP population, which is the primary analysis for efficacy, the rivaroxaban group had a lower event rate compared to that of the warfarin group (1.26 versus 2.61/100 patient-years, hazard ratio 0.49, [redacted]), resulting in approximately a 50% relative risk reduction.

Overall conclusions

This study demonstrated non-inferiority of rivaroxaban to warfarin for the primary safety endpoint, ie, the composite of adjudicated major bleeding and non-major clinically relevant bleeding events, in Japanese subjects with non-valvular atrial fibrillation. Rivaroxaban was also associated with a numerically lower rate of the composite of adjudicated stroke and non-CNS systemic embolism compared with warfarin in the per protocol, on-treatment population.

A34. The NICE final scope lists antiplatelet agents and dabigatran as comparators for rivaroxaban in people for whom warfarin is unsuitable. Please can you clarify your reasons for not covering these comparisons in this population within the submission?

The warfarin unsuitable group is considered in the submission and the most commonly used antiplatelet agent, aspirin is the comparator.

The NMA did not detect any significant differences in any endpoints between rivaroxaban and dabigatran, therefore a cost minimisation exercise was conducted. This analysis is applicable irrespective of the population considered – so no additional analysis was conducted in the warfarin unsuitable group.

A35. Please comment on the generalisability of the ROCKET AF trial to the UK population, including:

a. How similar are the event rates from the ROCKET AF trial to those in the UK atrial fibrillation patient population;

Unpublished GPRD analysis shows an incidence rate per 100 patient-years for the composite endpoint of [redacted] for patients on warfarin. This compares to a rate of 2.2 per 100 patient-years for

the warfarin arm in the safety on treatment analysis in ROCKET. This supports the generalisability of ROCKET to a UK population.

b. How similar are the characteristics of the patients in the ROCKET-AF trial to the atrial fibrillation patients of the UK.

Patients recruited to the ROCKET AF trial were those eligible for oral anticoagulation and with significant co-morbidity. The patients recruited to ROCKET AF were therefore not representative of the whole AF patient population in the UK but a group at significant risk of stroke and thromboembolic events. This is a strength of the study as the positive results were achieved in a group of patients with significant co-morbidity and elevated risk of stroke and thus can be considered a rigorous test of rivaroxaban.

Section B: Clarification on cost-effectiveness data

The ERG have requested consistency in the reporting of results (ERG question B3), and therefore all scenarios presented below are based on the point estimates of the different comparators used in the different analyses.

Results are presented for the base case population, the poorly controlled population and patients unsuitable to warfarin to summarize the requests from the ERG. Results are not presented for patients receiving no treatment as this option is always dominated by aspirin.

EXECUTIVE SUMMARY

Full population (SoT)

Base Case	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	8,200	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071	633	0.087	0.073	8,732	8,732
With bleed risk adjusted	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	8,994	9.212	6.992					
Rivaroxaban based on the ROCKET AF trial SoT data	8,366	9.304	7.068	628	0.092	0.076	8,259	8,259
With reduced AC monitoring costs in primary care	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	7,192	9.221	6.998					

Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071	1,642	0.087	0.073	22,645	22,645
With age-adjusted utilities	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	8,200	9.221	6.698					
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	6.765	633	0.087	0.067	9,420	9,420
With all adjustments combined	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	7,325	9.203	6.685					
Rivaroxaban based on the ROCKET AF trial SoT data based on the ROCKET AF trial SoT data	8,979	9.294	6.755	1,654	0.091	0.070	23,621	23,621

Poorly controlled (SoT)

Base Case	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071					
Warfarin based on the ROCKET AF trial SoT data	10,423	9.221	6.998	1,589	-0.087	-0.073	Rivaroxaban dominates	Rivaroxaban dominates
With bleed risk adjusted	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban based on the ROCKET AF trial SoT data	8,994	9.304	7.068					
Warfarin based on the ROCKET AF trial SoT data	10,616	9.212	6.992	1,662	-0.092	-0.076	Rivaroxaban dominates	Rivaroxaban dominates
With reduced AC monitoring costs in primary care	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	8,703	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071	131	0.087	0.073	1,805	1,805

With age-adjusted utilities	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	6.765					
Warfarin based on the ROCKET AF trial SoT data	10,423	9.221	6.698	£1,589	0.087	0.067	Rivaroxaban dominates	Rivaroxaban dominates
With all adjustments combined	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	8,853	9.203	6.685					
Rivaroxaban based on the ROCKET AF trial SoT data based on the ROCKET AF trial SoT data	8,979	9.294	6.755	126	0.091	0.070	1,798	1,798

ASA patients (SoT)

Base Case	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Aspirin based on NMA SoT	10,367	8.782	6.409					
Rivaroxaban based on NMA SoT	11,249	9.151	6.833	883	0.369	0.424	2,083	2,083
With bleed risk adjusted	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Aspirin based on NMA SoT	10,392	8.785	6.411					
Rivaroxaban based on NMA SoT	11,309	9.153	6.835	917	0.368	0.423	2,165	2,165
With reduced AC monitoring costs in primary care	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
N/A								
With age-adjusted utilities	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Aspirin based on NMA SoT	10,367	8.782	6.409					
Rivaroxaban based on NMA SoT	11,249	9.151	6.833	883	0.369	0.424	2,348	2,348

With all adjustments combined	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Aspirin based on NMA SoT	10,377	8.779	6.191					
Rivaroxaban based on NMA SoT	11,291	9.145	6.565	914	0.366	0.374	2,446	2,446

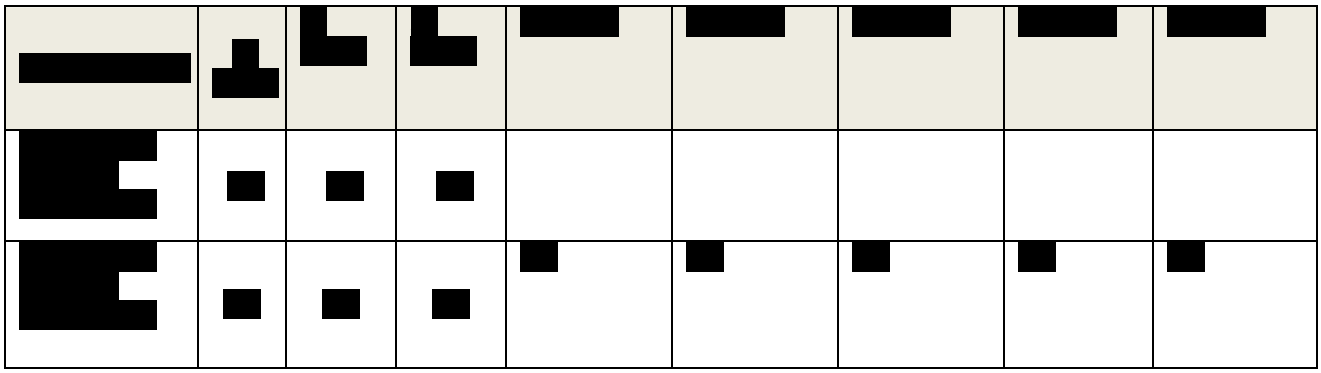
B1 **Priority request**: The model engine sheets show that the manufacturer intended to model different subgroups of patients within, below and above TTR ranges but ultimately presented results assuming all patients were within TTR ranges. The ERG requests a scenario analysis (including sensitivity analysis) incorporating the different proportions of patients in each TTR range observed in ROCKET AF.

In line with the ERGs request, we have provided data based on individual patient TTR (<60%, ≥60%). However bias may be introduced by using such data as patients in each cohort would invariably have different baseline characteristics. As such, these are not randomised cohorts and data should be interpreted with caution. For this reason the data are marked as commercial in confidence.

The ERG assumption that the submitted model assumes all patients to be within range is incorrect as the submitted model uses observed rates from ROCKET's warfarin arm, which is made up of patients distributed across the three INR control groups. The data values required to model according to INR from the ROCKET trial (and from literature, such as Hylek 2003) shows illogical trends in risk and were therefore not considered robust. However, to respond to the ERG request, the values adjusted for TTR observed in ROCKET and for a poorly controlled group are shown below.

The TTR from ROCKET assumes a distribution of 55.16% within, [redacted] and [redacted] range.

The poorly controlled group assumes a higher frequency of monitoring (36 visits/year) and a TTR of 40% within, 37% below and 23% above range. This is based on Gallagher 2011, which is a study using GPRD data and shows that the worst controlled quartile of patients were 40% in range. The distribution of above and below range were based on the ratio observed in a number of UK studies (Abdelhafiz 2004; Burton 2006; Evans 2000; Gallagher 2011; Jones 2005; Kalra 2000; Yousef 2004; pH Associates study (data on file)), though not necessarily for a 'poorly controlled' group.



PSA Results:

Table. Distribution of results in quadrants - TTR

	Dominant (SE)	Needs Evaluation (NE)	Inferior (SW)	Dominated (NW)
ICUR	15.4%	78.3%	0.5%	5.8%

Figure. CE Plot - TTR

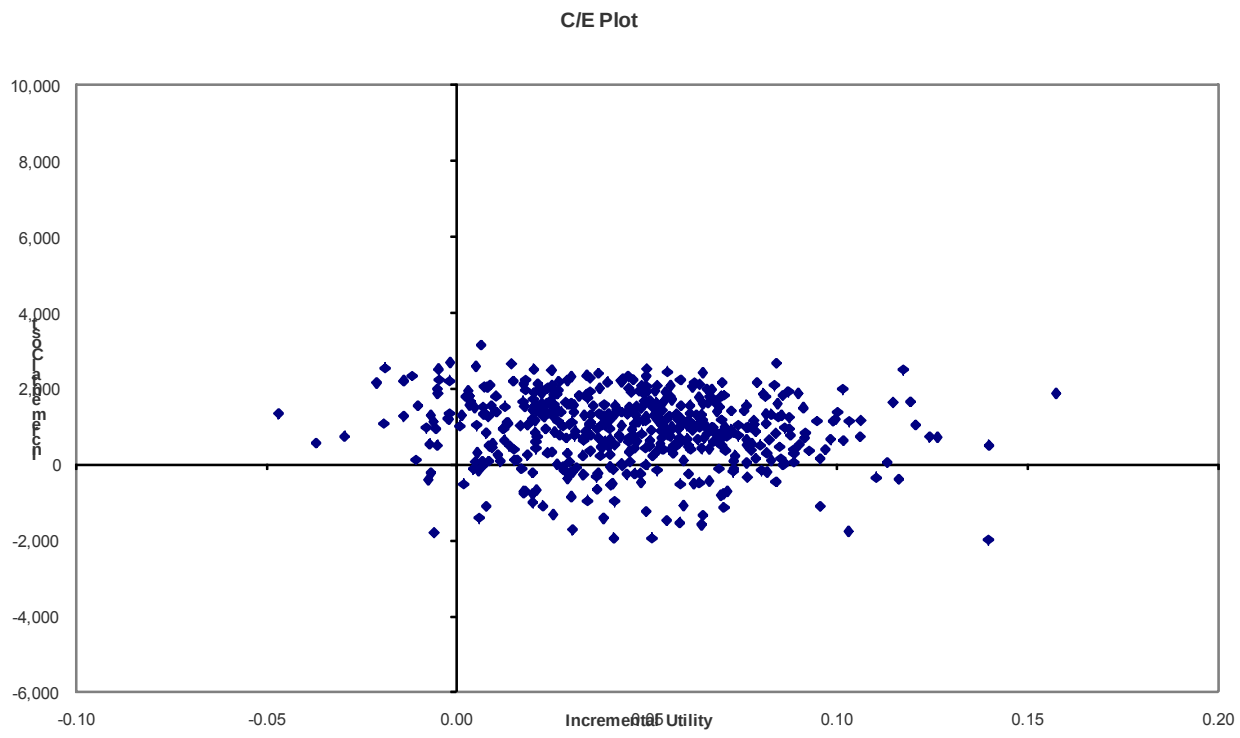
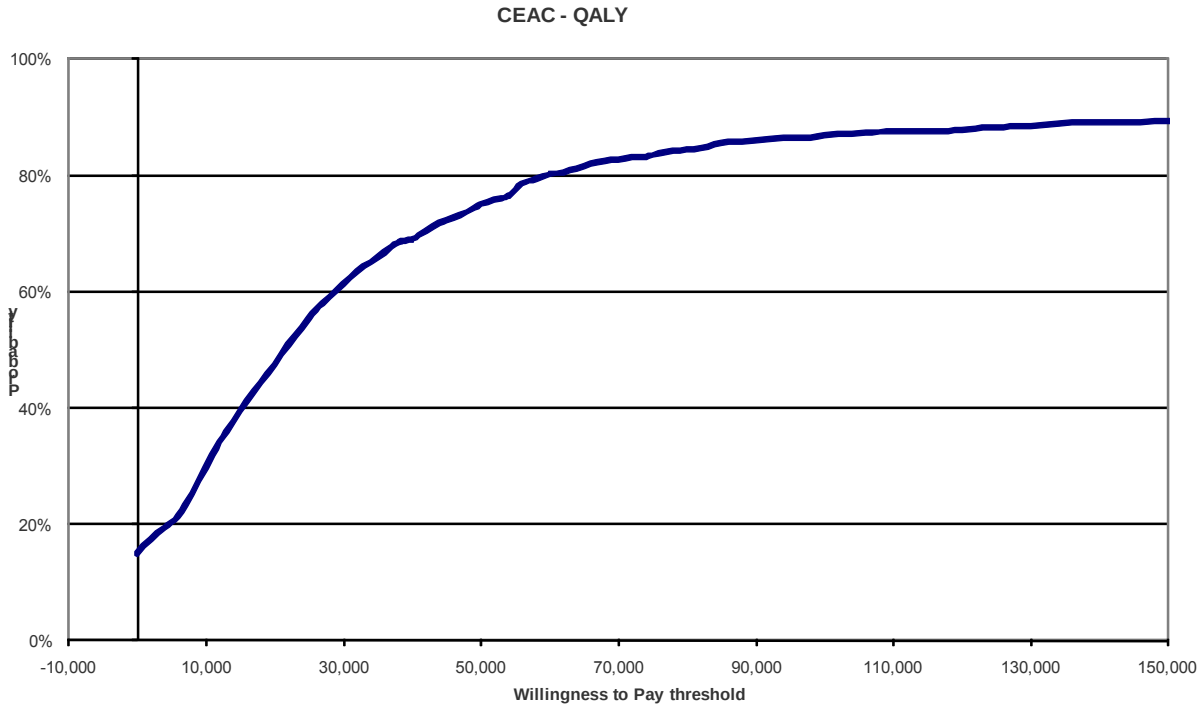


Figure. CEAC - TTR



B2 **Priority request**: The ERG requests that the manufacturer populates the following table with the different proportions of patients who are within, below and above TTR ranges in ROCKET AF trial.

The following table gives the percentage of INR values for warfarin.

% of INR values (mean)	SoT population
Within range (2-3)	55.16%
Below range <2	[redacted]
Above range >3	[redacted]

Imputed INR is calculated for the safety population on treatment using Point of Care device measurements. It is useful only for patients taking warfarin and thus it would not make sense to use off treatment data from the ITT population. In addition, the Point of Care device was not used in the off-treatment period. Therefore we feel it is not appropriate or relevant to provide this data.

B3 **Priority request**: For consistency across all comparisons the ERG requests that point estimates from the network meta-analysis should be used in the dabigatran deterministic analysis and that probabilistic sensitivity analysis be conducted i.e. present the cost effectiveness plane and the CEACs.

A deterministic analysis was conducted using point estimates of relative risks for clinical events in patients treated with dabigatran. Different relative risks were used for the 110mg and 150mg dose regimens, based on a network meta-analysis including data from the RE-LY trial. The analysis assumes that patients enter the model at age 73 on the 150mg dabigatran dose and switch to the 110mg dose at age 80, as specified in the EMEA license.

The results of the rivaroxaban vs dabigatran comparison presented below were generated using a revised version of the model which included the modifications described here in section B3, as well as those in B4 (age-adjusted bleed risk) and B7 (age-adjusted utilities). PSA was conducted on this revised model.

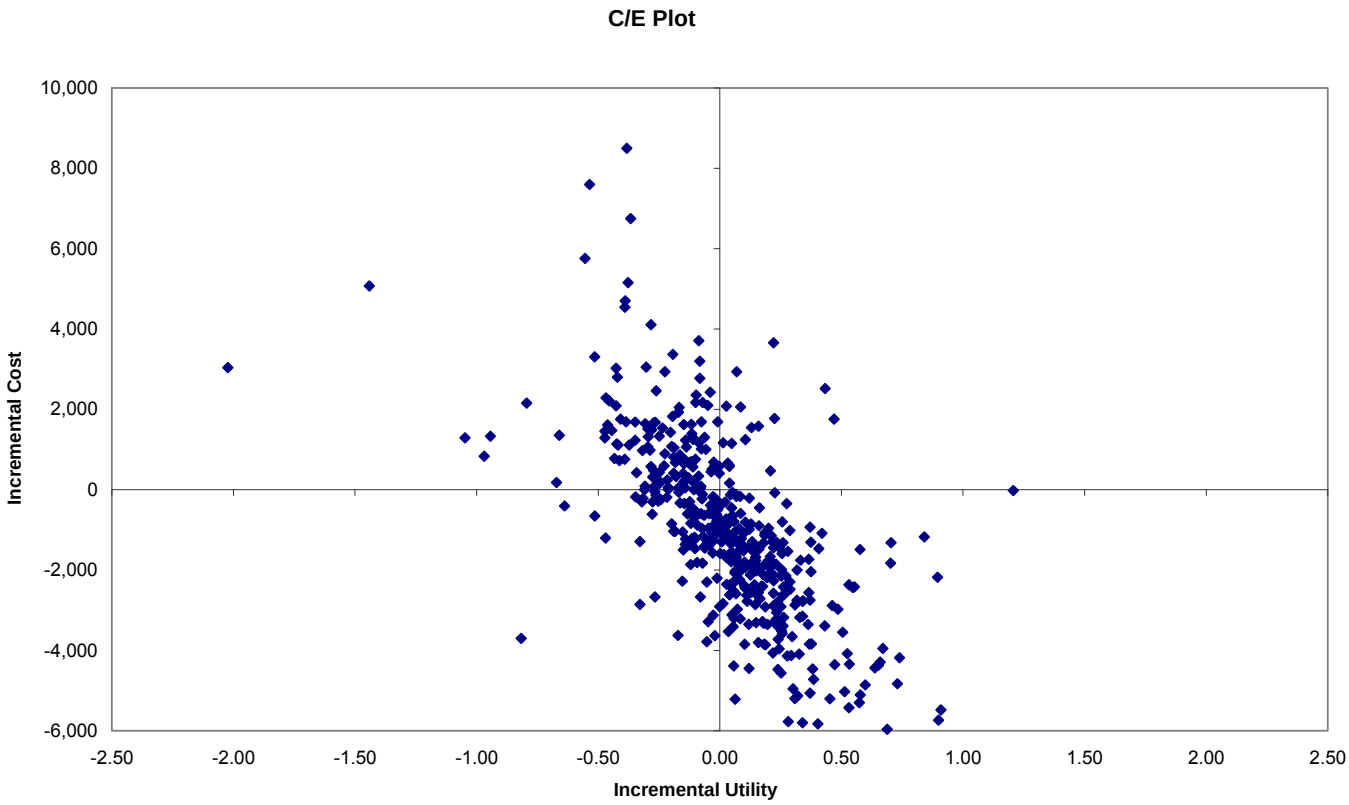
(This incorporates the age-adjusted bleed risk and utility values)	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Dabigatran (sequential) based on NMA data	13,241	9.048	6.461					
Rivaroxaban based on NMA data	12,430	9.049	6.463	-811	0.001	0.001	Rivaroxaban dominates	Rivaroxaban dominates

PSA Results

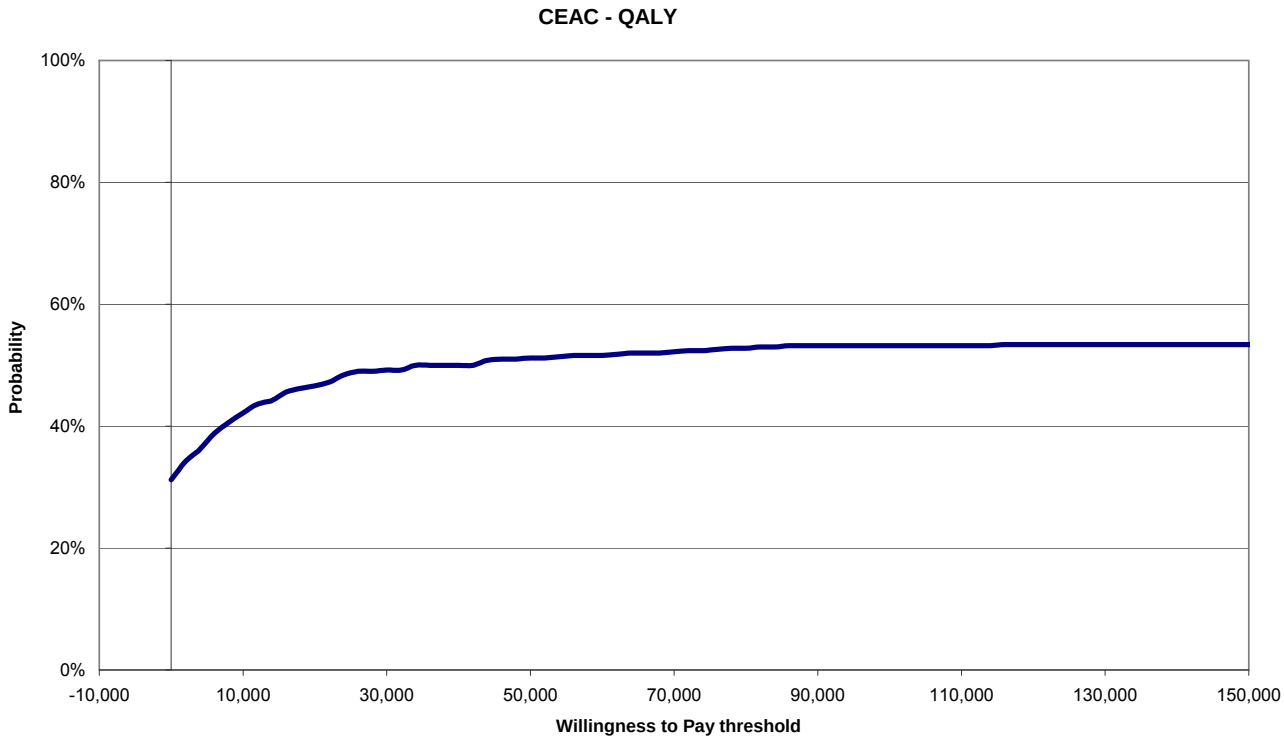
Table. Distribution of results in quadrants

	Dominant (SE)	Needs Evaluation (NE)	Inferior (SW)	Dominated (NW)
ICUR	51.4%	3.4%	20.2%	25.0%

C/E plot


C/E Plot
10,000
8,000
6,000
4,000
2,000
0
-2,000
-4,000
-6,000
Incremental Cost
-2.50
-2.00
-1.50
-1.00
-0.50
0.00
0.50
1.00
1.50
2.00
2.50
Incremental Utility

CEAC


CEAC - QALY
100%
80%
60%
40%
20%
0%
Probability
-10,000
10,000
30,000
50,000
70,000
90,000
110,000
130,000
150,000
Willingness to Pay threshold

B4 **Priority request**: Based on the evidence from the SAFE study (see table below) the ERG requests that bleeding risk is age adjusted in a similar manner to stroke and SE.

The model was modified to adjust the baseline rates of bleed events according to age. Data for relative gastrointestinal bleed rates in AF patients aged 65 and over were taken from the SAFE study (Hobbs et al., 2005) and applied to all bleed types included in the model. Note that because the mean patient age in the ROCKET trial was 73, the age-adjusted relative bleed rates were all normalised to a 73 year old population (eg 65 year olds were given a bleed rate of 1/1.2 times that observed in ROCKET).

Age	Gastrointestinal bleed (rate at age)
65	1
70	1.2
80	1.6
90	1.9

Source: Hobbs et al 2005 *A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study*

Compared to a base case ICER (using SoT data and point estimates), this revision has the following impact on the results:

Base Case	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	8,200	9.221	6.998					
Rivaroxaban	8,834	9.308	7.071	633	0.087	0.073	8,732	8,732
With bleed risk adjusted	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	8,994	9.212	6.992					
Rivaroxaban	8,366	9.304	7.068	628	0.092	0.076	8,259	8,259

B5 **Priority request**: The ERG requests a revised model in which dyspepsia is included as a side effect.

Bayer assumes that this request is due to dyspepsia being raised within the recent NICE appraisal of dabigatran in this indication. Whilst dyspepsia is an adverse event associated with dabigatran, it is not an adverse effect of note in the ROCKET AF trial. The manufacturer's submission for dabigatran states *"The only other adverse event that was significantly more common with DBG than with WFN was dyspepsia or gastritis-like symptoms (including abdominal discomfort)."*

When the table of the 15 most frequent treatment-emergent adverse events based on the rivaroxaban treatment group in the ROCKET AF trial is examined, dyspepsia is not listed [Supplement to: Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial

fibrillation. N Engl J Med 2011. DOI: 10.1056/NEJMoa1009638.] We have therefore not submitted a revised model in which dyspepsia is included as a side effect.

B6 **Priority request**: The ERG requests a scenario analysis which incorporates a cost of INR monitoring of £279.36 as recommended by the Appraisal Committee undertaking the appraisal of dabigatran *(The cost was taken from the CG 36, assumed that the new drugs will not totally replace warfarin, includes variable costs in primary care and total costs in secondary care, replaced 2004/05 reference costs with 2008/09 reference costs and inflated to 2009/10 prices*.).

The ERG has requested a scenario analysis which incorporated a cost of INR monitoring of £279.36 a year. The ERG included only variable costs in its estimate of monitoring costs in primary care. This is not standard practice in costing. Refer for example to Drummond et al "When … generalization of cost consequence to a national level is necessary, the use of average or integral costs [as opposed to marginal costs] is recommended".

> ***REF:*** *Drummond M and McGuire A "economic evaluation in health care: merging theory with practice", Oxford University Press 2001; page 71 section 4.2.4. This textbook is recommended reading for - as an example - those producing NICE guidelines (http://www.nice.org.uk/media/68D/29/The_guidelines_manual_2009_-_Chapter_7_Assessing_cost_effectiveness.pdf)*

However, further analysis has been conducted using variable costs only.

The mean annual number of INR monitoring visits per patient is 20, based on information reported in the Anticoagulation therapy service commissioning and benchmarking tool (NICE 2010). The ERG is therefore asking us to estimate the cost per visit to be £13.97 (£279.36 per year / 20 visits per year).

According to a survey of anticoagulation management by pH associates for the UK NHS in 2011 (ref #20 in MS), 34% of warfarin patients are managed in Secondary Care, and 66% in Primary Care.

The cost of an anticoagulation visit in secondary care in 2009/10 was £24.69 (National Schedule of Reference Costs Year 2009/10). We note that the 2008 Guide to the method of technology appraisals suggests that "A first point of reference in identifying such [NHS] costs and prices should be any current official listing published by the Department of Health and/or the Welsh Assembly Government", and specifically mentions HRG costs. We suggest that this costing is consistent with NICE methods.

For these figures to be consistent with an average cost of £13.97 across all visits requires the cost of a visit in primary care to be £8.84 (table below).

Table average cost per anticoagulation visit: ERG assumptions

Setting	Proportion of visits	Cost per visit (£)
Secondary care	34%	24.69
Primary care	66%	8.84
Weighted average		13.97

We note that the cost of reagents to conduct an INR test is £3 (NICE 2010).

Hence for the ERG cost of £279.36 to be consistent with all the evidence quoted, the cost of a primary care visit would be £5.84 (£8.84 total cost - £3 cost of reagents).

The PSSRU – the standard reference source for primary care costs in UK economics evaluations – estimates the fully allocated cost of a GP surgery consultation to be £36, of a GP telephone consultation to be £22, of a nurse consultation to be £12 and of a nurse procedure to be £10.

An INR test in primary care requires that staff make an appointment, draw blood, send off the test, obtain results, calculate any dose adjustment, communicate back to the patient and prescribe any new tablets required. We suggest that a cost of £5.84 for this process is implausibly low. We have however performed the analysis as requested by the ERG.

The manufacturer has also conducted a scenario analysis in which the proposed £279.36 - £13.97 per visit - refers only to Primary Care monitoring (assuming the cost per visit in Secondary Care is appropriately estimated in the National Schedule of Reference Costs Year 2009/10). We note that this cost is still lower than the cost of the reagents (£3) plus a singe GP nurse contact (£12).

Base Case	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin based on the ROCKET AF trial SoT data	8,200	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071	633	0.087	0.073	8,732	8,732
With alternative AC monitoring costs (£279.36/20 = £13.97) in primary care	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	7,192	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071	1,642	0.087	0.073	22,645	22,645

An additional scenario analysis was conducted to asses the impact of the alternative cost proposed by the ERG in a subgroup of the indicated population, who are not well controlled on

warfarin and therefore require frequent monitoring visits (3 visits per month, section 6.9.1 in the MS).

Base Case – poorly controlled	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071					
Warfarin based on the ROCKET AF trial SoT data	10,423	9.221	6.998	1,589	-0.087	-0.073	Rivaroxaban dominates	Rivaroxaban dominates
With alternative AC monitoring costs (£279.36/20 = £13.97) in primary care – poorly controlled	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin based on the ROCKET AF trial SoT data	8,703	9.221	6.998					
Rivaroxaban based on the ROCKET AF trial SoT data	8,834	9.308	7.071	131	0.087	0.073	1,805	1,805

B7 **Priority request**: The ERG requests that the manufacturer updates the main analysis with age adjusted utilities.

The model was updated to use different baseline utilities (for stable AF patients, not on therapy), depending on age. Patients aged 65-74 were assigned a base utility of 0.779 (Berg, et al., 2010), which is the value previously used for all ages. Patients aged 75 and above were assigned a base utility of 0.73 (Kind et al.). Because the value reported in the Kind study represents the UK population aged 75 and over, no further adjustments were required at more advanced ages.

Base Case	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Warfarin	8,200	9.221	6.998					
Rivaroxaban	8,834	9.308	7.071	633	0.087	0.073	8,732	8,732
With age-adjusted utilities	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	8,200	9.221	6.698					
Rivaroxaban	8,834	9.308	6.765	633	0.087	0.067	9,420	9,420

B8 Please explain the clinical rationale for each of the transitions in the table below, with particular reference to how and why patients are moving between on and off treatment health states.

Please see the table on the next page.

From	To	Rationale
Post minor stroke (on treatment)	Minor stroke (off treatment)	Patients in the post stroke state are still at risk to experience a further stroke (in fact their risk is elevated). Within the same 3 month cycle, the patient is also 'at risk' for discontinuing treatment. This transition combines the likelihood of these two events occurring.
Post minor stroke (on treatment)	Major stroke (off treatment)	
Post minor stroke (on treatment)	IC bleed - untreated	Patients in the post stroke state are still at risk to experience an IC bleed. In the same 3 month cycle, the patient is also 'at risk' for discontinuing treatment. This transition combines the likelihood of these two events occurring.
Post major stroke (on treatment)	Minor stroke (off treatment)	Patients in the post stroke state are still at risk to experience a further stroke (in fact their risk is elevated). Within the same 3 month cycle, the patient is also 'at risk' for discontinuing treatment. This transition combines the likelihood of these two events occurring.
Post major stroke (on treatment)	Major stroke (off treatment)	
Post major stroke (on treatment)	IC bleed - untreated	Patients in the post stroke state are still at risk to experience an IC bleed. In the same 3 month cycle, the patient is also 'at risk' for discontinuing treatment. This transition combines the likelihood of these two events occurring.
AC initiation	Minor stroke (off treatment)	From a state of AC initiation with anti-thrombotic therapy a patient can discontinue and have an event (minor/major stroke, IC bleed or SE) in the same 3month cycle. This transition combines the two likelihoods.
AC initiation	Major stroke (off treatment)	
AC initiation	IC - untreated	
AC initiation	SE - untreated	
On Tx Stable	Minor stroke (off treatment)	From a state of stable AF with anti-thrombotic therapy a patient can discontinue and have an event (minor/major stroke, IC bleed or SE) in the same 3month cycle. This transition combines the two likelihoods.
On Tx Stable	Major stroke (off treatment)	
On Tx Stable	IC - untreated	
On Tx Stable	SE - untreated	
Post IC bleed (high risk)	Minor stroke (off treatment)	Patients in the post IC bleed state are still at risk to experience a further stroke (in fact their risk is elevated) and is also at further risk of an IC bleed. Within the same 3 month cycle, the patient is also 'at risk' for discontinuing treatment. This transition combines the likelihood of these two events occurring.
Post IC bleed (high risk)	Major stroke (off treatment)	
Post IC bleed (high risk)	IC - untreated	
Minor bleed – untreated	AC initiation	Once a patient experiences a bleed event and is untreated, clinical advice indicated that they would be re-initiated on antithrombotic therapy as they would be under the care of a physician for the acute treatment of their bleed event and their history of AF would trigger therapy.
Major bleed - untreated	AC initiation	

B9 The ERG requests that the manufacturer presents the results of the one-way sensitivity analysis of age and time horizon.

Results: Full population

Base Case (Age=73; time horizon = lifetime)	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	8,200	9.221	6.998					
Rivaroxaban	8,834	9.308	7.071	633	0.087	0.073	8,732	8,732
25 years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	8,172	9.200	6.983					
Rivaroxaban	8,803	9.286	7.055	631	0.086	0.072	8,785	8,785
20years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	7,953	9.031	6.860					
Rivaroxaban	8,568	9.111	6.927	615	0.080	0.067	9,160	9,160
15 years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	7,257	8.438	6.423					
Rivaroxaban	7,830	8.503	6.478	573	0.064	0.055	10,456	10,456
10 years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	5,775	6.996	5.348					
Rivaroxaban	6,270	7.034	5.381	495	0.038	0.034	14,649	14,649
Average age cohort: 65 years	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	10,420	11.861	8.986					
Rivaroxaban	11,215	12.009	9.106	795	0.148	0.120	6,652	6,652
Average age cohort: 78 years	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Warfarin	6,759	7.494	5.695					
Rivaroxaban	7,288	7.551	5.743	529	0.057	0.049	10,867	10,867

Results: Poorly controlled

Base Case (Age=73; time horizon = lifetime)	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban	8,834	9.308	7.071					
Warfarin	10,423	9.221	6.998	1,589	-0.087	-0.073	Rivaroxaban dominates	Rivaroxaban dominates
25 years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban	8,803	9.286	7.055					
Warfarin	10,389	9.200	6.983	1,586	-0.086	-0.072	Rivaroxaban dominates	Rivaroxaban dominates
20years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban	8,568	9.111	6.927					
Warfarin	10,130	9.031	6.860	1,562	-0.080	-0.067	Rivaroxaban dominates	Rivaroxaban dominates
15 years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban	7,830	8.503	6.478					
Warfarin	9,307	8.438	6.423	1,477	-0.064	-0.055	Rivaroxaban dominates	Rivaroxaban dominates
10 years time horizon	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban	6,270	7.034	5.381					
Warfarin	7,539	6.996	5.348	1,269	-0.038	-0.034	Rivaroxaban dominates	Rivaroxaban dominates
Average age cohort: 65 years	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban	11,215	12.009	9.106					
Warfarin	13,163	11.861	8.986	1,948	-0.148	-0.120	Rivaroxaban dominates	Rivaroxaban dominates
Average age cohort: 78 years	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus baseline (QALYs)**	**ICER (£) incremental (QALYs)**
Rivaroxaban	7,288	7.551	5.743					
Warfarin	8,632	7.494	5.695	1,344	-0.057	-0.049	Rivaroxaban dominates	Rivaroxaban dominates

B10 Please give the clinical rationale for the absence of a post systemic embolism health state.

Systemic embolism as a clinical event was considered to be important to include in the model as it could have significant clinical consequences as well as being part of the primary endpoint of the ROCKET trial. However, the long-term consequences of a systemic embolism are dependent on the location of the emboli and have wide variation in terms of costs and quality-of-life implications. The reasons for not including a post-systemic embolism state were two-fold. Firstly, there is little to no data to quantify the economic costs and quality-of-life (utilities) of long-term sequelae for a systemic embolism. Secondly, the number of events observed is too low for meaningful estimations to be calculated for the distribution of embolic events by location, which would allow for a weighted calculation of the outcomes by emboli type. The low number of events also indicates that the impact of including such a state would be minimal.

B11 The ERG requests that data from England and Wales should be used as far as is applicable. In the post stroke state, independent of therapy, the rates were derived from an Italian study (MS ref 92). Please can the manufacturer explain why UK data sources such as the Oxford Vascular Study (OXVASC) were not used?

One publication from the OXVASC study was returned in the systematic review of the literature conducted to inform the model inputs. However, this was excluded as it was not an atrial fibrillation population. The ERG refers to an alternative to MS ref 92 Marini et al, which gives rates of post-stroke death with long term follow-up (10 years+). The OXVASC publication reporting on death rates (Rothwell et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study)) does not report death rates post-event for use in this parameter.

B12 Please explain the discrepancy between the number of papers from which data have been extracted and the number of papers identified (as indicated by the flow diagram). For instance, quality-of-life papers retrieved should be 16 but the extraction accounts for 12 papers (MS table 48 pg 173)

The review for quality-of-life papers were conducted in two separate streams as indicated by the flow diagram in Figure 18 of the MS. The first focused on utility values associated with the event and the second focused on utility values associated with treatments. These found 20 and 28 studies respectively. Table 46 lists these studies minus the 4 which were duplicates between the two streams.

The full-text of the 48 papers were reviewed and 14 total were selected for data extraction. (5 from the event arm of the search, 11 from treatment arm, 1 additional paper added from review of references; 3 of these 17 papers were excluded as duplicates).

Figure 18 in the MS represents the search described above to the identification of these 14 papers.

In addition, an update of the literature review conducted in May 2011 to cover May 2010 to May 2011 ultimately identified 5 papers for data extraction once a similar procedure as above was conducted on the update search hits.

In total, 19 studies (14 from the initial search and 5 from the update search) were available for data extraction.

The search strategy for utilities dictated that data would only be extracted from an original source paper. Therefore, of the 14 papers from the initial search, 6 were included as they were original studies. The 8 excluded papers either did not specify where they sourced their utilities from or they referenced one of the 6 included papers (total from initial: 6 papers). Similarly, of the 5 papers from the update search, only 2 were original source papers while the 3 which were excluded referenced either the 6 included from the initial or the 2 included from the update (total from update: 2 papers).

In the update literature search it became apparent that no papers were found which fit the inclusion criteria for certain health states. Therefore, 3 additional papers were included in the update report as providing the best available 'proxy' data in the absence of data which fit the inclusion criteria (revised total from update: 2 papers + 3 'proxy' papers = 5 papers).

In conclusion, this leads to the 11 final papers (6 from the initial search and 5 from the update search) listed in Table 48 of the MS.